

Figure 1

VSQGSINSGDYXWSWRQHPKGLDCIGXYSSSTYYNPSIKSRVTISVDISKNOFLKLTSYTAADTAVVYCARSTVNPNGWDEPWGGGTLVTSS (SEQ ID NO:3)
CDR1 CDR2 CDR3

Figure 2

GTCTCTGGTG GCTCCATCAA CAGTGGTGA TACTACTGGA GCTGATCCG CCAGCACCCA GGAAGGGCC TGGACTGCAT TGGGTACATC TATTACAGTG GGAGCAGCTA
CTACAACCCG TCCCTCAGA GTCCAGTTAC CATATCAGTA GACACGCTA AGATCAGTT CTTCCTGAAG CTGACCTCTG TGA CTGCCC GGACACGGCC GTGTATTACT
GTCCGAGATC TACGGTGGA ATCCGGGGT GGTTCGACCC CTGGGGCCAR GGAACCTGG TCACCGTCTC CTCA (SEQ ID NO:4) 3

Figure 3

TTTCQASODINNNXLNWFQOKPKGKAPKVLHHDASNLETGSPSRFSGSGTDEFTTISGLOPEDIATYYCQOYESLPLTFGGGTVKIKRTVAAPSVFIHPPSDEQ (SEQ ID NO:5) 24
CDR1 CDR2 CDR3

Figure 4

ACCATCACTT GCCAGGCGAG TCAGAGACATT AACAACTATT TAAATTGGTT TCAGCAGAAA CCAGGAAAG CCCCT AAGTTCCTGA TCCAGCATGC ATCCAATTG
GAAACAGGGG GCCCATCAAG GTTCAGTGA AGTGATCTG GGACA GATTTACTT TCACCATCAG CGGCTGCAAG CCTGAAGACA TTGCACACATA TTAATTGCAA
CAGTATGAAA GTCTC CCACTCACTT TCGGCGGAGG GACCAAGTG GAGATCAAA (SEQ ID NO:6) 7

09107603 : 110509

Figure 5

VSQGSINsgDyywswrOHpGKLEWIGSlyysgNtFYNESLKSRYTSLDTSKNOESLKSSTVAADTAVCYCARNVTTGAEDIWQGTMTVSS (SEQ ID NO: 7) 25
CDR1 CDR2 CDR3

Figure 6

GTCTCTGTG GCTCCATCA CAGTGGTGT TACTACTGA GCTGATCCG CCAGCACCCA GGAAGGCC TGGAGTGAT TGGTCCATC TATTACAGTG GGAACACCTT
CTAACACCCG TCCCTCAGA GTCGAGTTAC CATATCACTA GACACGCTA AGAACCAAGT CTCCTGAAG CTGAGTTCTG TGA CTGCCCG GACACACGCC GTGTGTTACT
GTGCGAGAAA TATAGTACT ACGGCTGCTT TTGATATCTG GGGCCAAAGG ACAATGGTCA CCGTCTCTTCA (SEQ ID NO: 8) 25

Figure 7

TTTCQASODLTLVNWYXOOKPGKAPKLLINDASSLETGVPLRFSSGSGTIDETFTIISLOPEIDIAITYYCCQXDHLPLTFGGGTKVAKRTVAAPSVFIHPPSDEQ (SEQ ID NO: 9) 26
CDR1 CDR2 CDR3

Figure 8

ACCATCACTT GTCAGGCGAG TCAGGACATT ACCATTATT TAAATTGGTA TCAACAGAAA CCAGGGAAG CCCCCT AAGCTCCTGA TCAACGAGCG ATCCAGTTTG
GAAACAGGGG TCCCATTAAG GTTCAGTGA AGTGATCTTG GGACA GATTTTACTT TCACCATCAG CAGCCTGCAG CCTGAAGATTA TTGCAACATA TTA CTGTCAA
CAGTATGATC ATCTC CCGCTCACTT TCGGCGGCGG GACCAAGGTG GCGATCAAA (SEQ ID NO: 10) 26

Figure 9

VSGGSISSG**D**xyxw**L**wirohpgkgl ewigylyxsg**N**tyynpsl ksrsv**S**msl**D**ts**E**noefsl klsvtl adtavyvycarkpyl tggedymgqgtlvtvss (SEQ ID NO:11) **27**

CDR1

CDR2

CDR3

Figure 10

GTCTCTGGTG GCTCCATCAG CAGTGTGAT TACTACTGA CCTGGATCCG CCAGCACCCA GGAAGGGCC TGGAGTGGAT TGGGTACATC TATTACAGTG GGAACACCTA
CTACAAACCCG TCCCTCAAGA GTGAGTTTC CATGCAATA GACACGCTCG AGAACCAAGT CTCCCTGAAG CTGAGCTCTG TGAAGTCCGC GGACACGGCC GTGTATTACT
GTGCGAGAAA ACCAGTGAAG GGGGGGAGG ACTACTGGGG CCAGGGAACC CTGGTCACCG TCTCTCA (SEQ ID NO:12) **28**

Figure 11

TTTQASODISNYL NWYOOKPKAPKLLIYDASNL HTGVPSRFSGSGSDTDTETISSLOPEDIVGyyVooYEsL PCGFQQT KLEIKRTVAAPSVHFPSPDEQ (SEQ ID NO:13) **28**

CDR1

CDR2

CDR3

Figure 12

ACCATCACTT GCCAGGGCAG TCAGACATT AGTAAGTATT TAAATTGGTA TCAGCAGAAA CCAGGGAAG CCTT AAGTCCCTGA TCTACGATGC TTCCAATTG GAAACAGGGG
TCCCATCAAG GTTCAGTGA GTGATCTG GGACA GATTTTACTT TCACCATCAG CAGCTGCAG CTGAAGATG TTGGAACATA TGTCTGTCAA CAGTATGAGA GTCTC
CCGTGCGGTT TTGGCCAGGG GACCAAACTG GAGATCAAA (SEQ ID NO:14) **29**

09197503 : 440599

Figure 13

VS~~GS~~IN~~SG~~DFYWSWROHPKGLEMIGYXSGTYNPSLKSRVTMSIDPSKNOFSLKISVTADTAVVYCATSLYYGGMDVWGQGTTVTSS (SEQ ID NO:15)

CDR1

CDR2

CDR3

Figure 14

GTCTCTGTG GCTCCATCAA CAGTGTGAT TTCTACTGGA GCTGATCCG CCAACACCA GGAAGGGCC TGGAGTGGAT TGGTACATC TATTACAGTG CGAGCACCTA
CTACAACCCG TCCCTCAAGA GTCGAGTTAC CATGTCAATA GACCCGTCTA AGAACGAGTT CTCCCTGAAA CTGATCTCTG TGA CTGCCCC GGACACGGCC GTTATTACT
GTGCGACNTC CCTTACTAT GCGGGGGGTA TGGACGTCTG GGGCCAAGG ACCACGGTCA CCGTCTCTC A (SEQ ID NO:16)

Figure 15

TTTCQASODISNNNLNWYOOKRGNAPKLIYDASNLETGVPSRFSGSGTDETFTISNLOPEDIATYYCOHYDHLPWTFGQGTKVEXKRTVAAPSVFIPPSDEQ (SEQ ID NO:17)

CDR1

CDR2

CDR3

Figure 16

ACCATCACTT GCCAGGCGAG TCAGACATT AACAACTATT TGAATTGGTA TCAGCAGAGG CCNGGGAACG CCCCT AACTCCTGA TCTACGATGC ATCCAATTG
GAACAGGGG TCCCATCAAG GTTCAGTGA AGTGATCTG GGACA GATTTTACTT TCACCATCAA CAGCTGCAG CCTGAAGATA TTGCGACATA TTATTGTCAA
CACTATGATC ATCTC CCGTGGACGT TCGGCCAAGG GACCAAGGTG GAANTCAA (SEQ ID NO:18)

Figure 17

VSQGSINNGDYYWSVIRHPGKGLFWIGHUYSGSTYYLPSLSKRLTISYDTSKNQPSLKLNSYTAADTAVVYTCARGIVTTYEDYMGQGTIVTVSS (SEQ ID NO:19)

CDR1

CDR2

CDR3

Figure 18

GTCTCTGCTG GCTCCATCAA CAATGGTGAT TACTACTGGA GCTGGATCCG CCAGCACCCCA GGGAAAGGCC TGGAGTGAT TGGGCACATC TATTACAGTG GGAGCACCCTA CTACATCCCG TCCCTCAAGA GTCGAAGTAC CATATCAGTA GACACGTCTA AGAACAGGT CTCCTGAAG CTGAAGTCTG TGACTGCCGC GGACACGGCC GTGTATTACT GTGCGAGAGG GACAGTAACT ACGTACTACT TTGACTACTG GGGCCAGGGA ACCCTGGTCA CCGTCTCTC A (SEQ ID NO:20)

Figure 19

TTTCRASQSSSYLNWYOOKPGKAPKLLIYAASLQSGVPSRSGSGGIDFTLTISLOPEDFATYYCGQGYRTPECSFGQGTKLEIKRTVAARSVHFPSPDEQ (SEQ ID NO:21)

CDR1

CDR2

CDR3

Figure 20

ACCATCACTT GCCGGGCAAG TCAGAGCATT AGCAGCTATT TAAATTGTA TCAGCAGAAA CCAGGGAAG CCCCCT AAGCTCCTGA TCTATGCTGC ATCCAGTTTG CAAAGTGGGG TCCCATCAAG GTTCAGTGGC AGTGATCTG GGACA GATTTCACATC TCACCATCAG CAGTCTGCAA CCTGAAGATT TTGCAACTTA CTACTGTCAA CAGGTTACA GAACC CCTCCGGAGT GCAGTTTGG CCAGGGGACC AAGCTGAGA TCAAA (SEQ ID NO:22)

12

Figure 21

VSGSVSSG D Y Y W S R O P G K L E W I G H L Y S G N I N Y N S L K S R V T I S L D I S K N O F S L K S S V T A D I V Y C A R D E L T G S E D Y W G Q G T L V T S S (SEQ ID NO:24) **33**

CDR1 CDR2 CDR3

Figure 22

GTCCTGCTG GCTCCGTCAG CAGTGGTGAT TACTACTGGA GCTGATCCG GCAGCCCCA GGAAGGAC TGGAGTGAT TGGACATCTC TATTACAGTG GGAACACCA
CTACAACCCC TCCCTCAAGA GTCGAGTCAC CATATCATTA GACACGTCCA AGAACAGTT CTCCTGAAG CTGAGCTCTG TGACCGCTGC GGACACGGCC GTGTATTACT
GTGCGAGAGA TTTTGTGACT GGTCCTTCT TTAGTACTG GGGCCAGGA ACCCTGTCA CCGTCTCTC A (SEQ ID NO:25) **2**

Figure 23

TTTCQASDISNYL N W Y O O K P G K A P K L I N D A S D L E T G V P S R I S G S G T D F T I S N L O P E D I A T Y C O Y D S L P L F G G T K V E R R T V A A P S V H P P S D E Q (SEQ ID NO:26) **2**

CDR1 CDR2 CDR3

Figure 24

ACCATCACTT GCCAGGCGAG TCAGGACATA AGCAACTATT TAAATTGTA TCAGCAGAAA CCAGGAAAG CCGCT AAGCTCCTGA TCAACGATGC ATCCGATTTG
GAAACAGGGG TCCCATCAAG GATCAGTGGA AGTGATCTG GGACA GATTTACTT TCACCATCAG CAACCTGCAAG CCTGAAGATA TTGCAACATA TTAGTGTCAA
CAATATGATA GTCTC CCGCTCACTT TCGCGGAGG GACCAAGGTG GAGATCAGA (SEQ ID NO:27) **2**

Figure 25

VSGGSV **X**SGD YXXWSWIRPPGKGLEWIGYDYXSGTNNYNPSLKSRYVTISVDTSKNQSLKLSSTVAADTA VVYVCARDSLGATINXWGQGLVTIVSS (SEQ ID NO:28) **35**
CDR1 CDR2 CDR3

Figure 26

GTCTCTGTGTG GCTCCGCTCTA CAGTGGTGAT TACTACTGGA GCTGGATCCG GCAGCCCCCG GGAAGGAGC TGGAGTGGAT TGGGTATATC TATTACAGTG GGAGCACCAA
TTACAATCCC TCCCTCAAGA GTCGAGTAC CATATCAGTA GACACGTCCA AGAACCAGTIT CTCCCTGAAG CTGAGCTCTG TGACCGCTGC GGACACGGCC GTGTATTACT
GTCCGAGAGA CTCCATACTG GGAGCTACCA ACTACTGGGG CCAGGGAACC CTGGTCACCG TCTCTCTCA (SEQ ID NO:29) **15**

Figure 27

TTTCASO **X**ISNYL **X**WYQOKPGKAPK **X**LSDASNIETGVPSRFSGSGGT **X**XITITISLQPEDIAITYH **X**OYXS **X**LPLTFGGGTVKVEIKRTVAAPSVFIPPPSDEQ (SEQ ID NO:30) **25**
CDR1 CDR2 CDR3

Figure 28

ACCATCACTT GCCAAGCGAG TCNGACAATT AATACTAATT TANATTGGTN TCACGAGAAA CCAGGGAAG CCCT AASTCTCTGA TCTCCGATGC ATCCAATTTA
GAAACAGGGG TCCCATCGAG GTTCAGTGGA AGTGATCTTG GGACA GANTNTACTT TCACCATGAG CAGCCTGCAG CCTGAAGATA TTGCNACATA TCACTGTCNA
CAGTATNATA GTCTC CCGCTCACTT TCGGCGGAGG GACCAAGGTA GAGATCAAA (SEQ ID NO:31) **19**

Figure 29

VSGGSVSSGDyywTwiroSSpkGLEWIGHuyysgNnnynpsLksrLtislDtskTofslKLssVTADTAlyyCVRDRVYGAEDJWGQTMVTSS (SEQ ID NO:32)

CDR1

CDR2

CDR3

37

Figure 30

GTCTCTGGTGGCTCCGTCAGCAGTGTGAT TACTACTGGA CCTGGATCCG GCAGTCCCA GGAAGGGAC TGGAGTGGAT TGGACACATC TATTACAGTG GGAACACCAA
TTATAACCCC TCCCTCAAGA GTCCACTCAC CATATCAATT GACACGTCCA AGACTCAGTT CTCCCTGAAG CTGAGTCTTG TGACCGCTGC GGACACGGCC ATTATTTACT
GTGTCGAGA TCGAGTGA CTGGCTTTTG ATATCTGGGG CCAAGGACA ATGGTCACCG TCTCTTCA (SEQ ID NO:33)

17

Figure 31

TTTCQASODISNNYLNWYOOKPKGAPKLLYDASNLEIGVPSRHS~~SGSGCIDDET~~ISSLOPEDATYFCOHEHDLPLAFGGGTVKVEIKRTVAAPSVHFPSPDEQ (SEQ ID NO:34)

CDR1

CDR2

CDR3

45

Figure 32

ACCATCACTT GCCAGGCGAG TCAGGACATC AGCACTATT TAAATTGGTA TCAGCAGAAA CCAGGGAAG CCCCT AAACCTCCTGA TCTACGATGC ATCCAATTTG
GAAACAGGGG TCCCATCAAG GTTCAGTGA AGTGATCTG GGACA GATTTACTT TCACCATCAG CAGCTGCAG CCTGAAGATA TTGCAACATA TTCTGTGCAA CACTTTCATC
ATCTC CCGCTCGCTT TCGGCGGAGG GACCAAGGTG GAGATCAA (SEQ ID NO:35)

28

09197593 : 110509

Amino Acid Sequences and Structure of Human Heavy Chain Derived from EGFR-Specific Hybridomas

| Human $\gamma 2$ | CDR1 | CDR2 | CDR3 | ASTKGPSVFPPPLAPCSRSTST |
|------------------|--|-------|--------------|------------------------|
| 4-31 | VSGGSISGGYYWSWIRQPPGKLEWIGYIYVSGSTYYNPSLKSRVTISVDTSKNQFSLKLSVTAADTAIVYYCAR | | | |
| E1.1 | ---N-D--- | DC | STVNPG WFDP | WGQGYLVTVSS |
| E2.4 | ---N-D--- | S-N-F | NIVTTG AFDI | WGQGTMTVTVSS |
| E2.5 | ---D-T--- | N | KPTGG EDY | WGQGTMTVTVSS |
| E6.2 | ---N-DF--- | N | TSLYYGG GMDV | WGQGTMTVTVSS |
| E6.4 | ---NN-D--- | H-I | GTVTYY YFDY | WGQGTMTVTVSS |

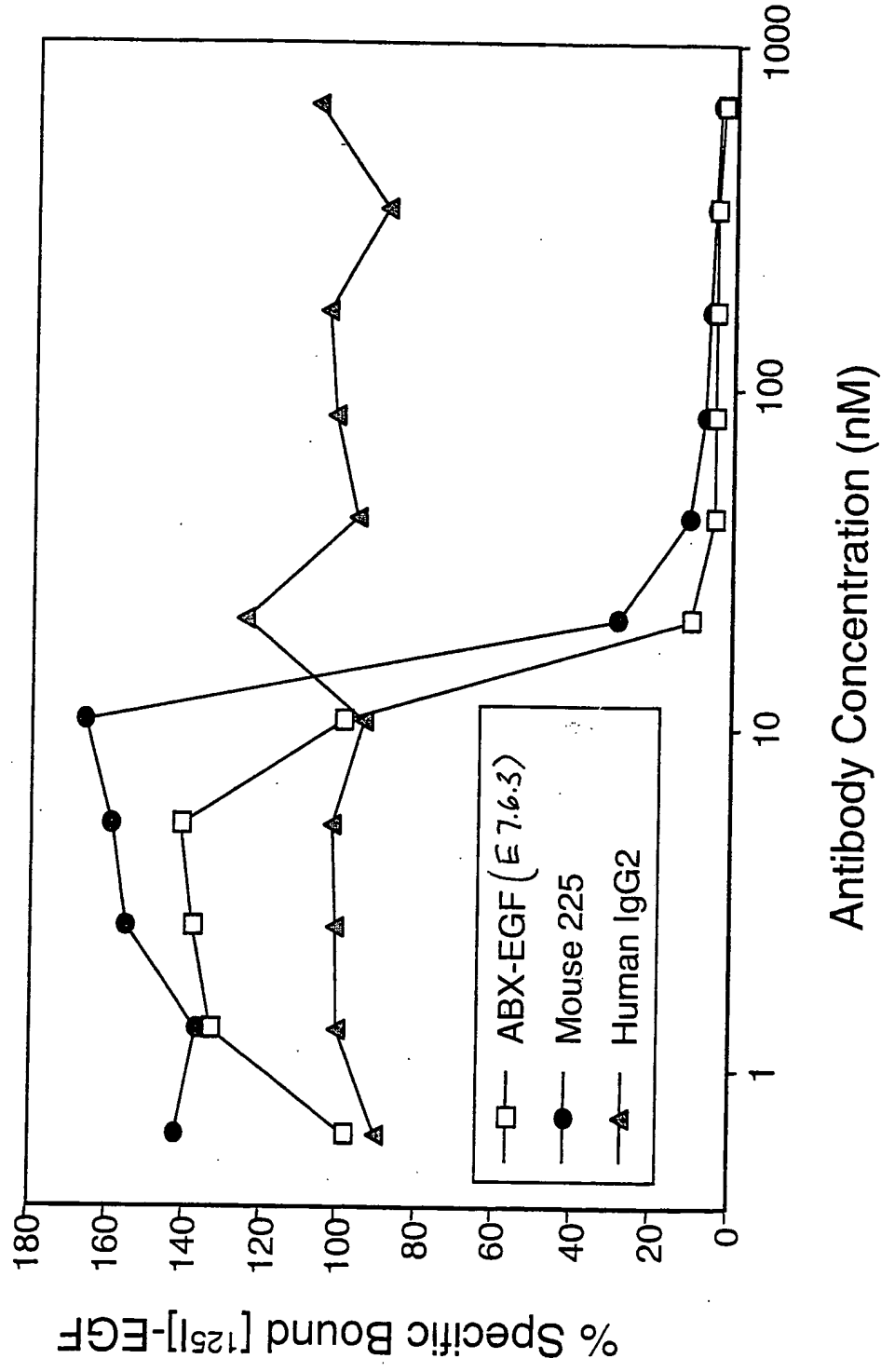
| Human $\gamma 2$ | CDR1 | CDR2 | CDR3 | ASTKGPSVFPPPLAPCSRSTST |
|------------------|--|------|-------------|------------------------|
| 4-61 | VSGGSISGGYYWSWIRQPPGKLEWIGYIYVSGSTYYNPSLKSRVTISVDTSKNQFSLKLSVTAADTAIVYYCAR | | | |
| E2.11 | ---D--- | HL-N | DFLTGSF FDY | WGQGTMTVTVSS |
| E6.3 | ---Y-D--- | | DSILGA TNY | WGQGTMTVTVSS |
| E7.6.3 | ---D-T--- | H-N | DRVTGA FDI | WGQGTMTVTVSS |

SECRET

Amino Acid Sequence and Structure of Human Kappa Chain Derived from EGFR-Specific Hybridomas

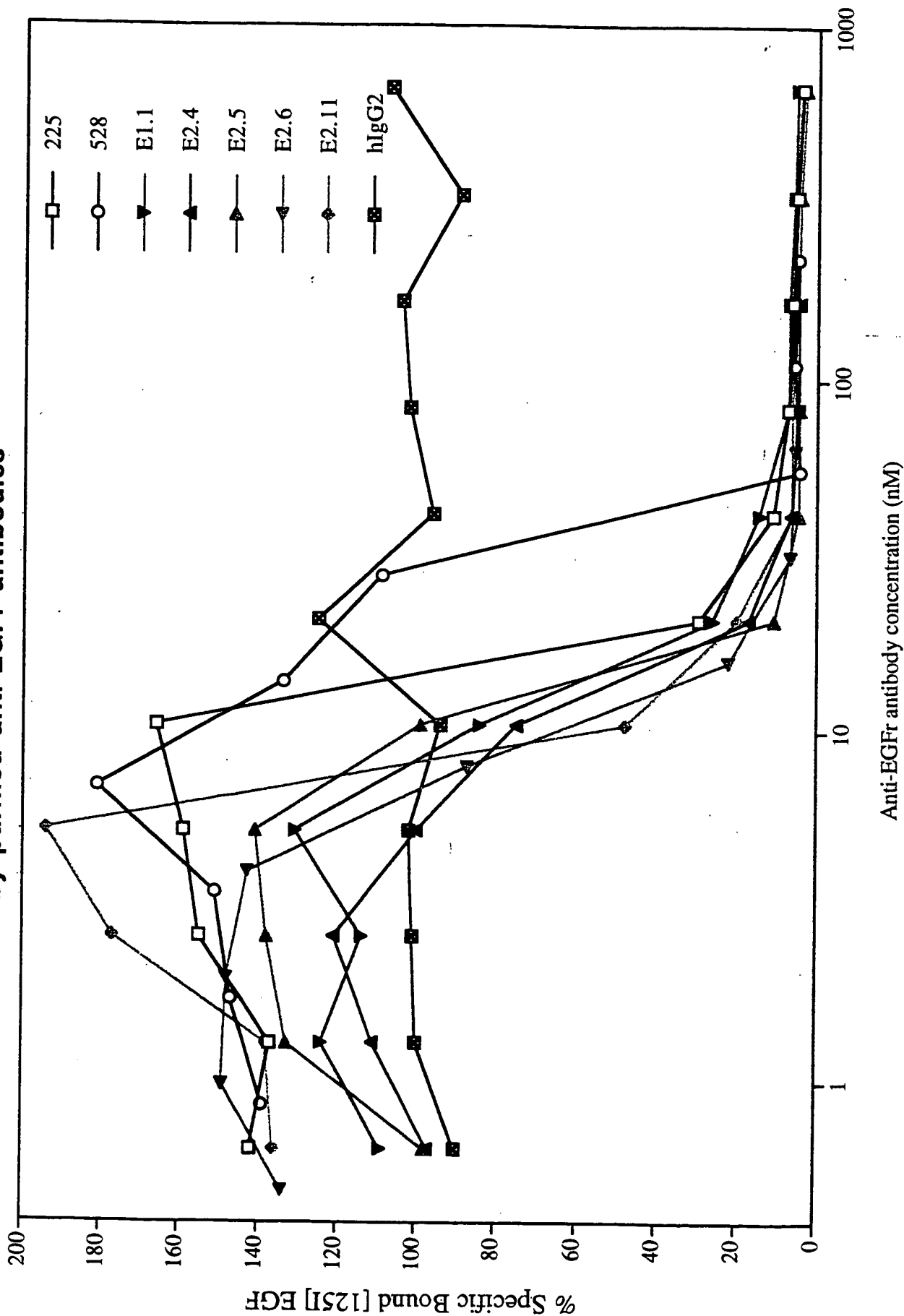
| V _K CDR1 | V _K SEGMENT | | J _K SEGMENT | CDR3 |
|---------------------|---|------------|------------------------|---------|
| | CDR1 | CDR2 | | |
| V _K (12) | TITCOASQDISVILNWTQOKPGKAPKLLIYDASNLETVPSPRFGSGSGTDFFTISSLPEDIAITYCQYDNL | | RTVAAPSVFIFPPSDEQ | |
| Human Ck | | | | |
| EGF.1.1.K | N--F--V--H--G-- | G-- | LTFGGKVEIK | ES-- |
| EGF.2.4.K | TI--N--S--L-- | N--S--L-- | LTFGGKVAIK | H-- |
| EGF.2.5.K | | | CGFGGKLEIK | ES-- |
| EGF.2.11.K | | N--D--I-- | LTFGGKVEIR | S-- |
| E6.2.K | N--R--N-- | N--N-- | WTFQGGTKVEIK | H--H-- |
| E6.3.K | X--N--X-- | X--S-- | LTFGGKVEIK | XS-- |
| E6.4.K* | R--S--S-- | A--S--QS-- | CSFGGKLEIK | GYRT-PE |
| *012 gene | | | LAFGGKVEIK | HF-H-- |
| E7.6.3.K | | | | |

ABX-EGF: Blockage of EGF Binding to Human Epidermoid Carcinoma A431 Cells



66507 66543 66

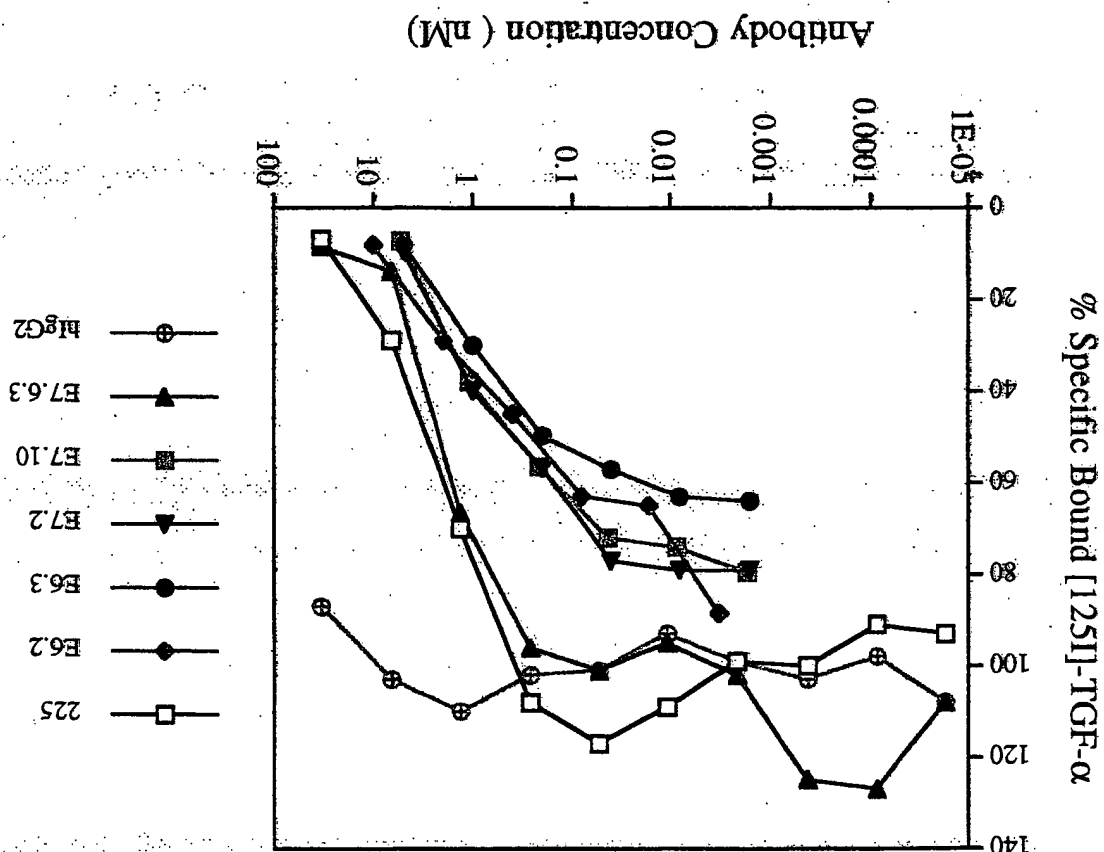
Inhibition of EGF binding to EGF receptors on A431 cells by purified anti-EGFr antibodies



Background=0.1nM [125I]EGF=1016 cpm

Figure 37

Inhibition of TGF- α binding to A431 cells
by anti-EGF receptor antibodies



09107593-110599

Figure 38

ABX-EGF: Blockage of EGF Binding to Human Colon Adenocarcinoma SW948 Cells

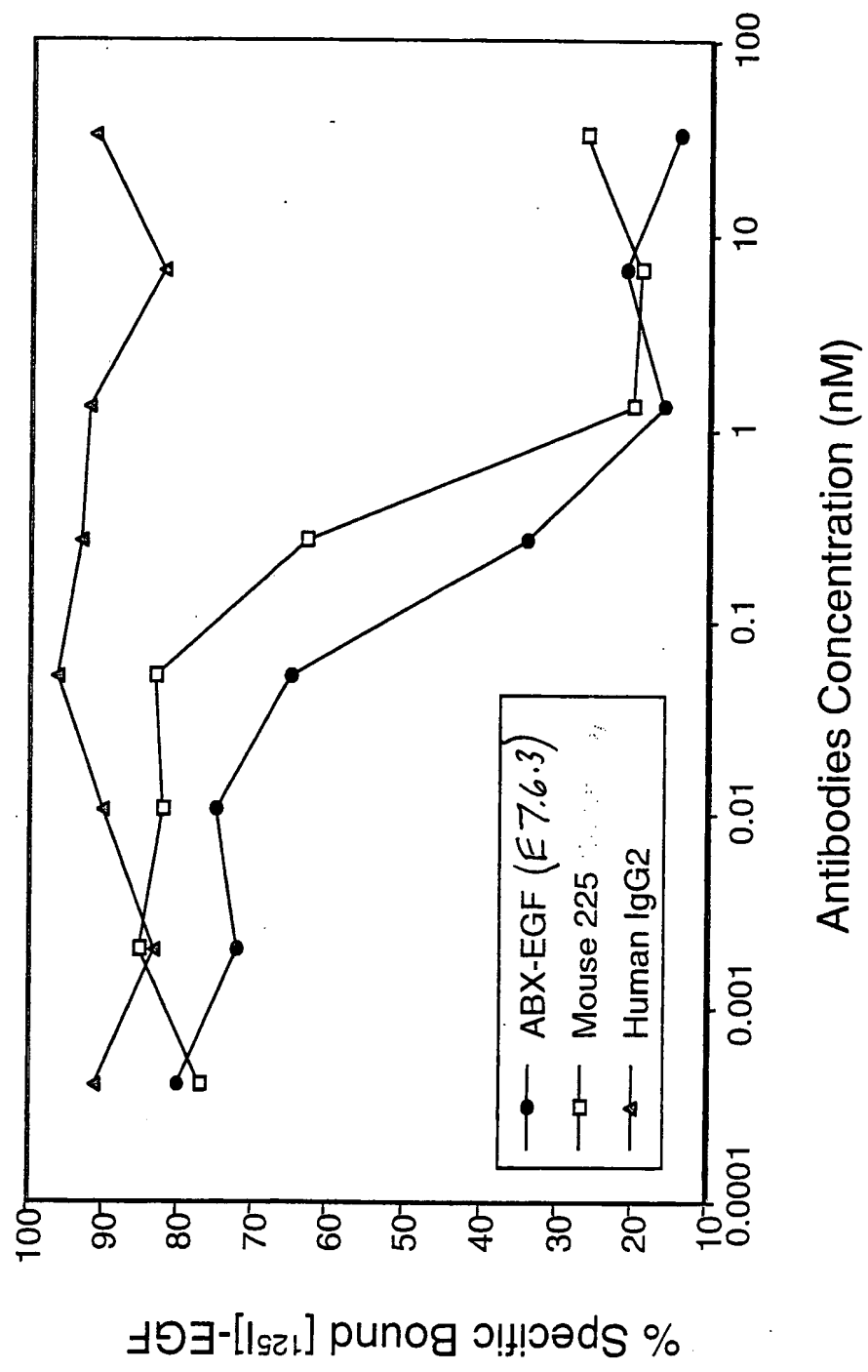
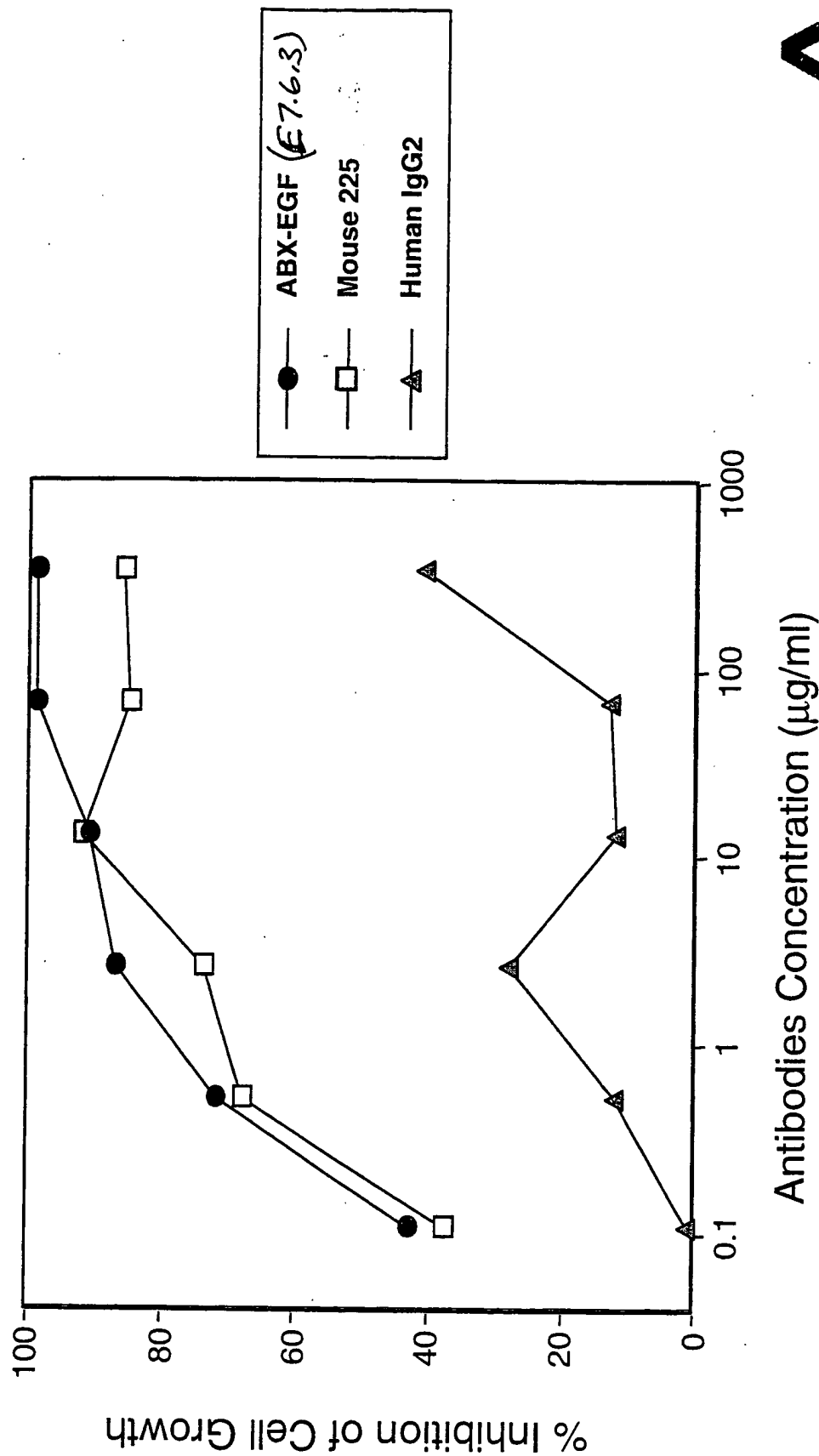
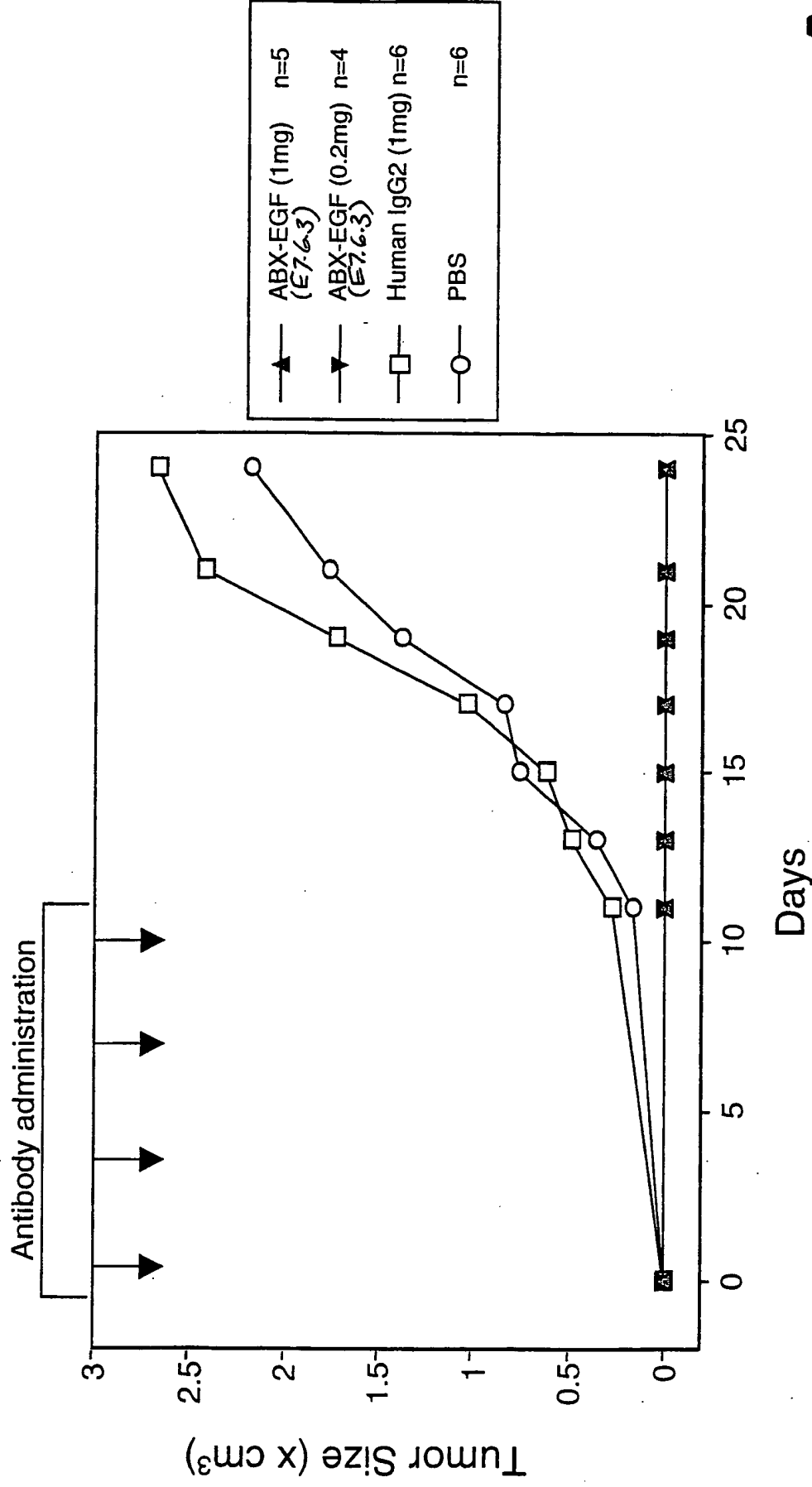


Figure 39

ABX-EGF: Inhibition of Human Colon Adenocarcinoma (SW948) Growth *In Vitro*



ABX-EGF: Inhibition of Human Epidermoid Carcinoma Growth in Nude Mice



5 x 10⁶ A431 cells injected at day 0



Figure 41

Inhibition of Human Epidermoid Carcinoma Formation in Nude Mice by ABX-EGF

| Treatment | Dose (mg) | Tumor Formation ^b (incidence) | Tumor size ^c (cm ³) |
|-------------------------|-----------|--|--|
| PBS | | 6/6 | 1.376 |
| Human IgG2 ^a | 1 | 6/6 | 1.727 |
| E7.6.3 | 1 | 0/5 | 0 |
| | 0.2 | 0/4 | 0 |
| E2.5 | 1 | 0/3 | 0 |
| | 0.2 | 0/3 | 0 |
| E1.1 | 1 | 0/3 | 0 |

^a control human myeloma IgG2

^b incidence determined 19 days post tumor inoculation

^c tumor size measured 19 days post tumor inoculation



ABX-EGF: Prevention of Human Tumor Formation in Nude Mice

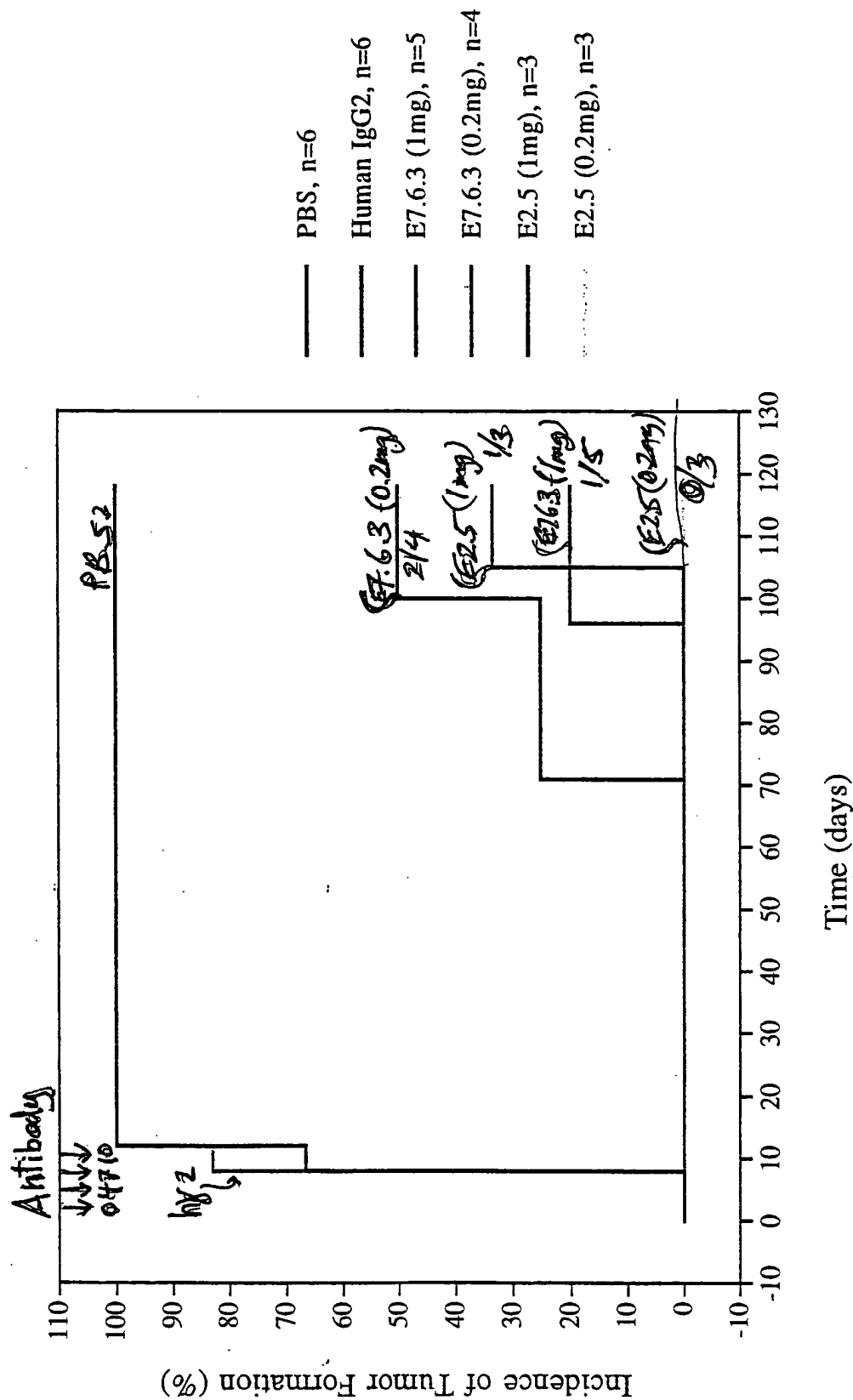
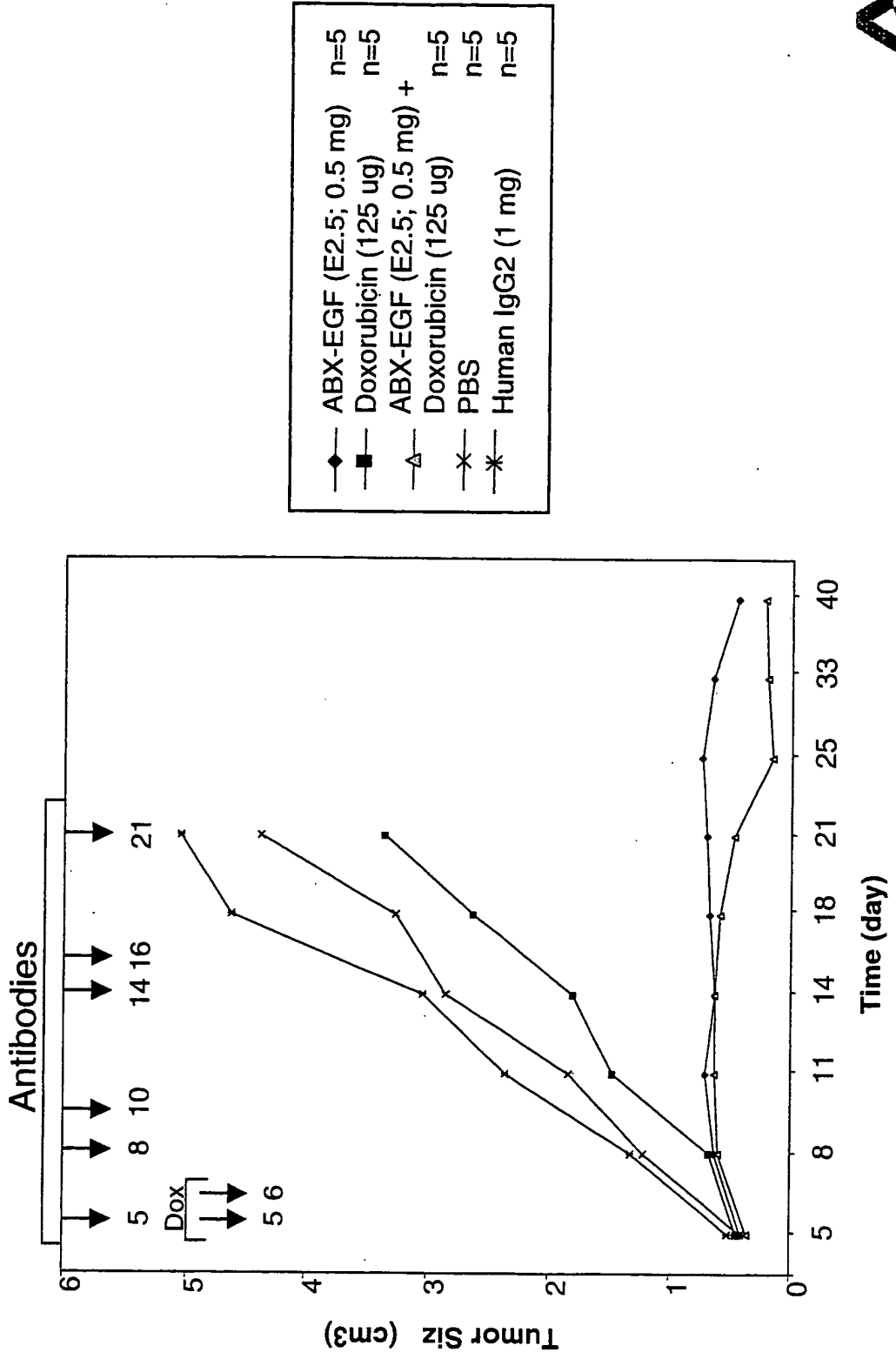
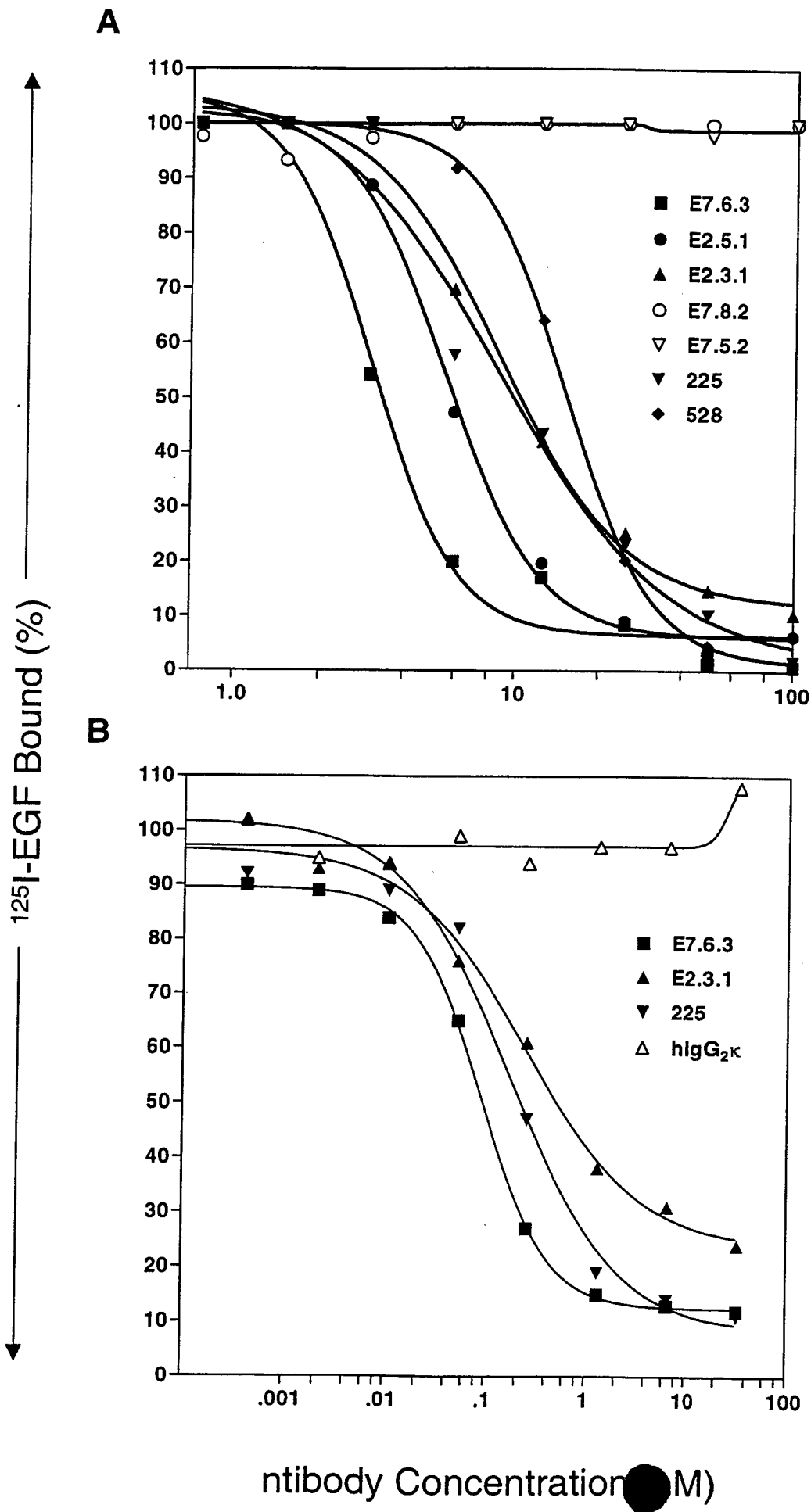




Figure 44

Eradication of Established Human Epidermoid Tumor in Nude Mice by ABX-EGF (E2.5)

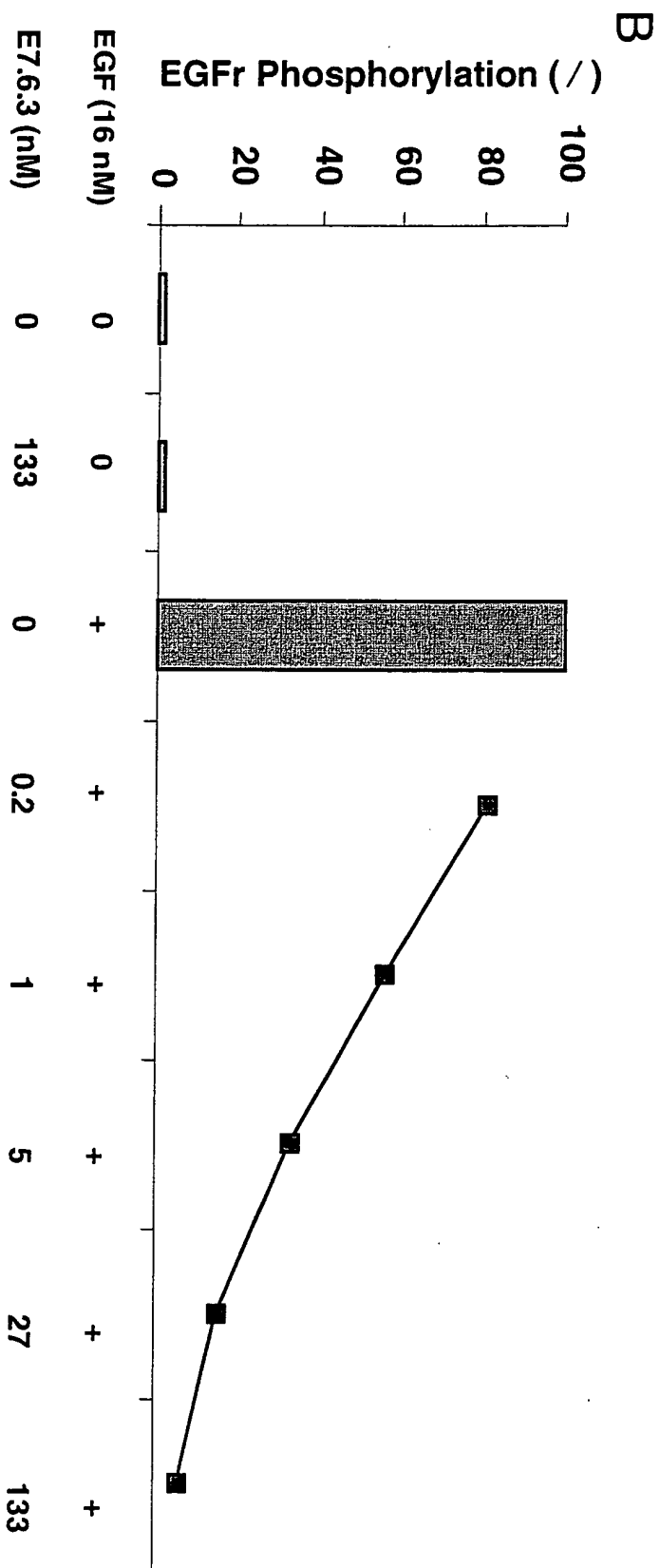
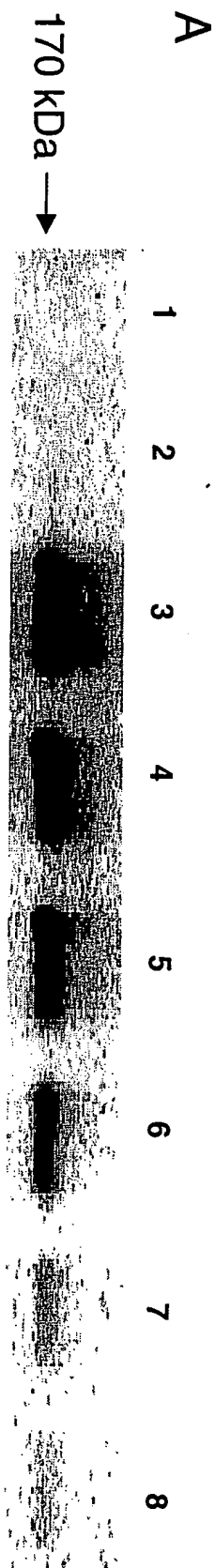




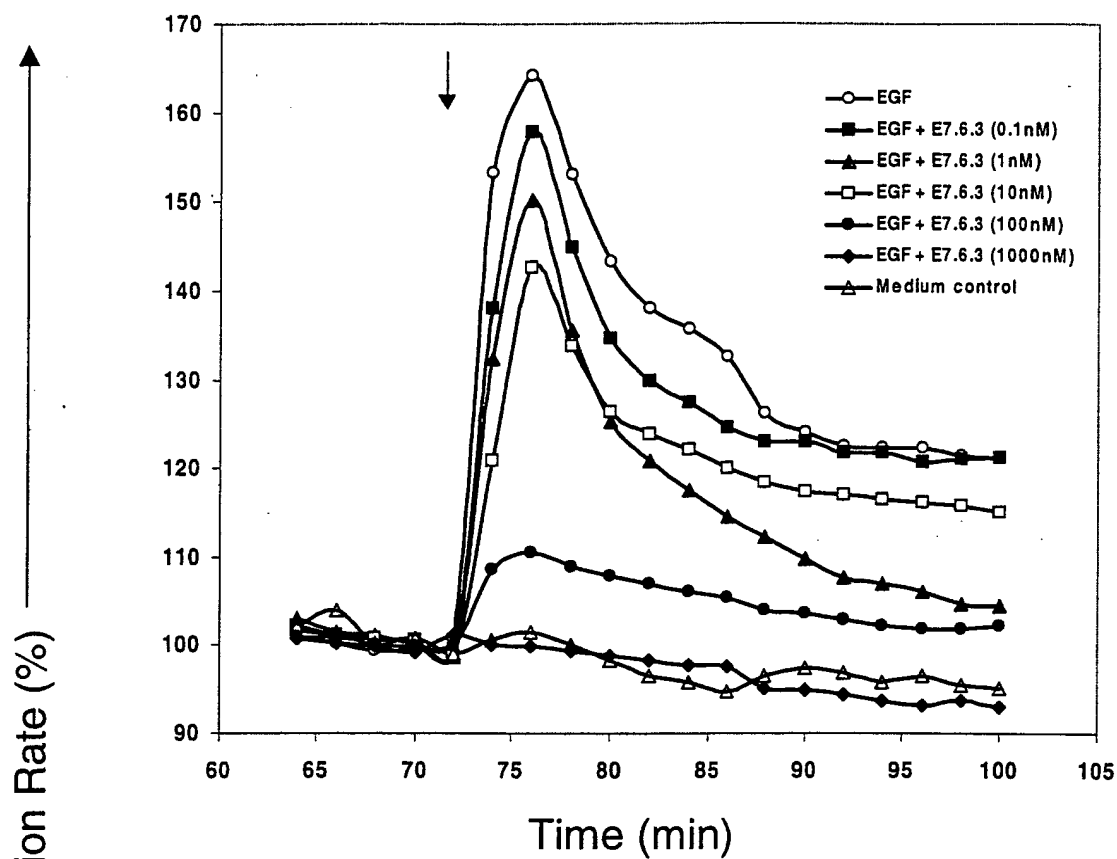
66501: 652670

Fig. 46

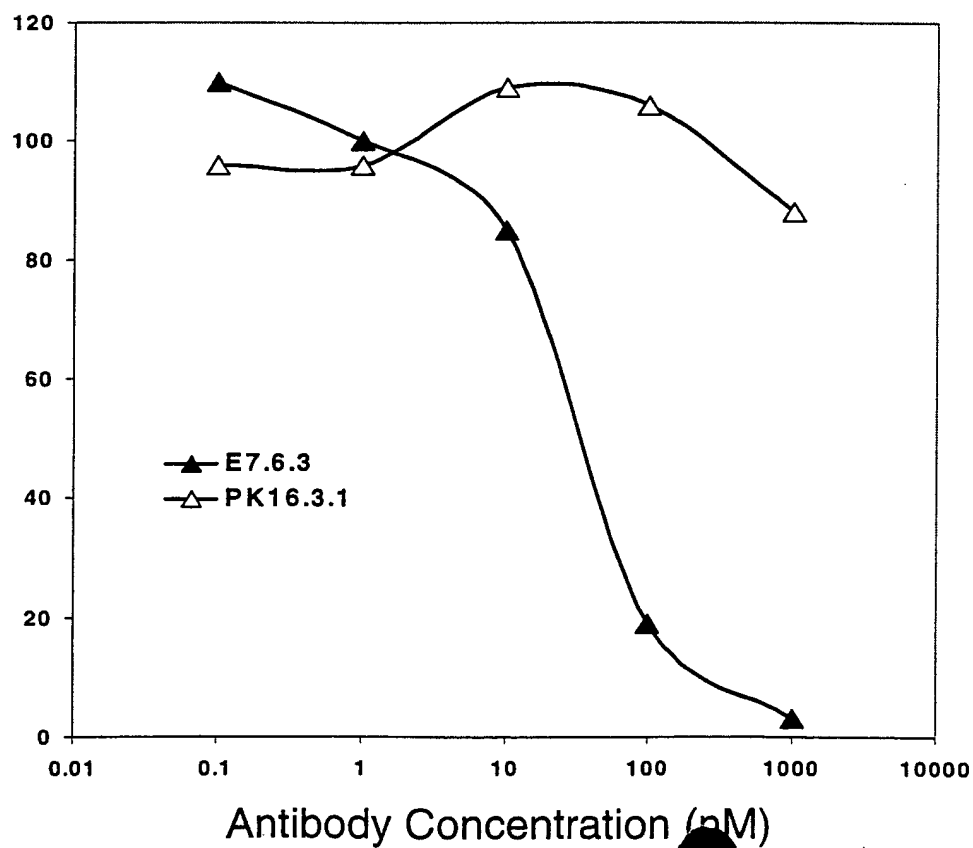
665017-EGF/EGFR

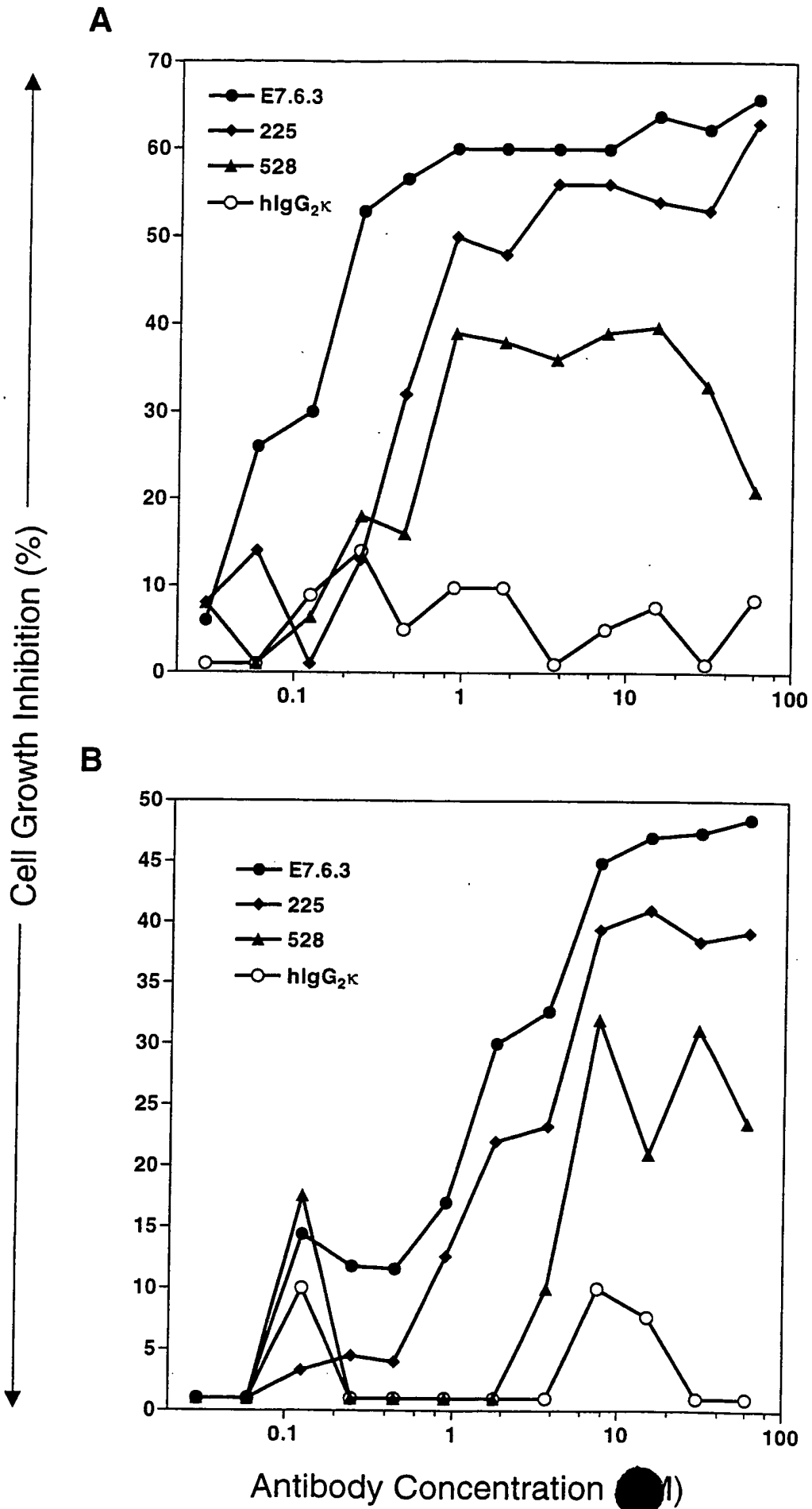


A



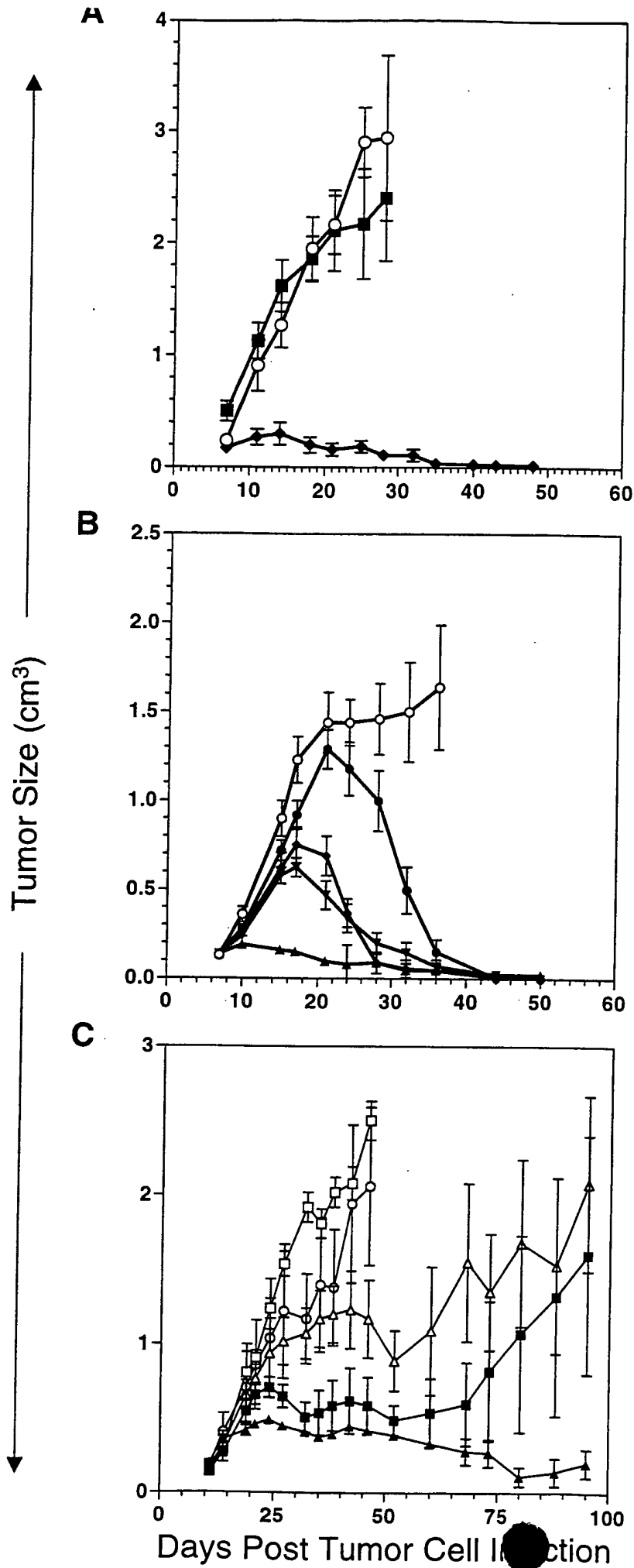
B





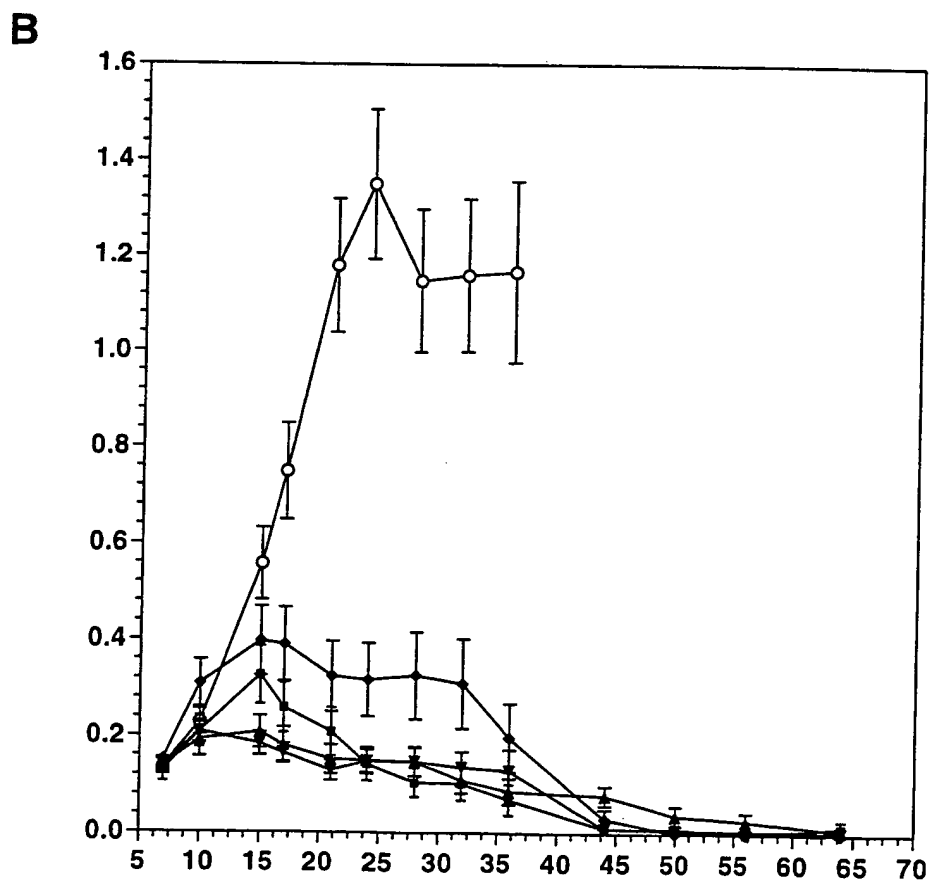
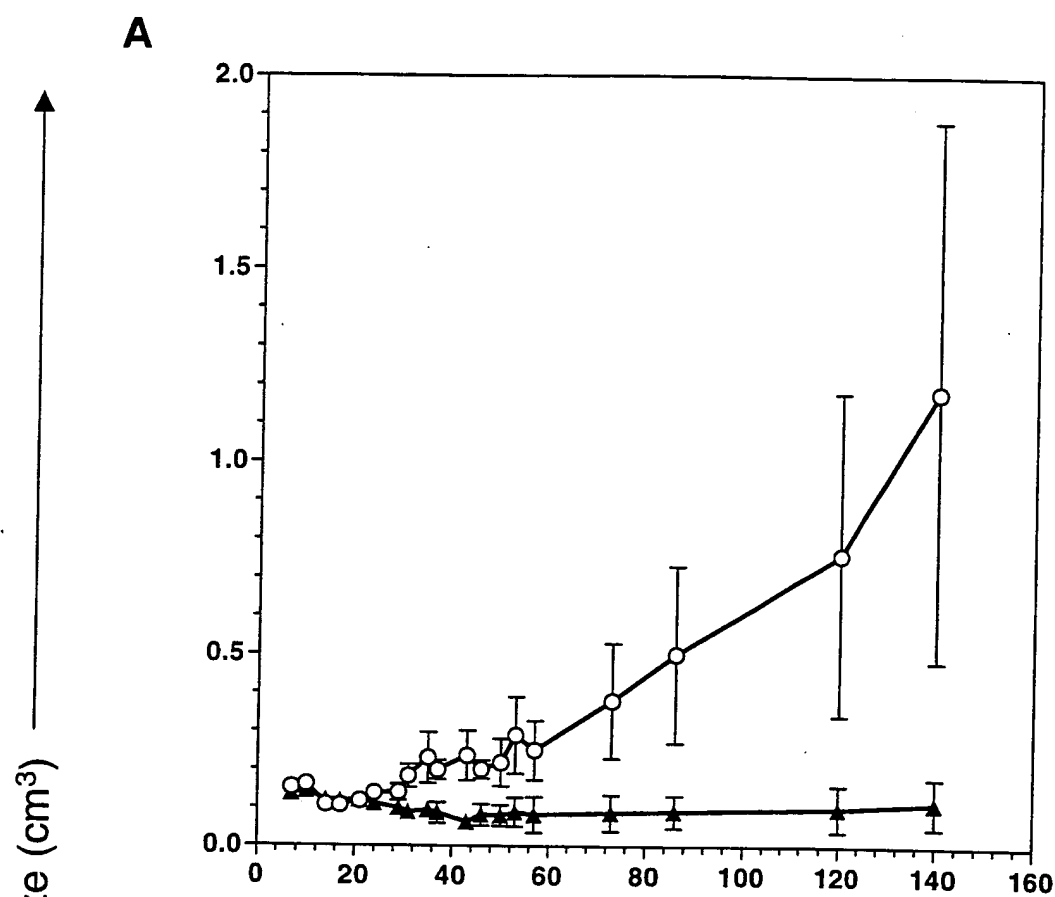
00107593-410598

Fig. 49



00197593-110599

Fig. 50



Days Post Tumor Cell Inoculation

00197593-110598

6=50

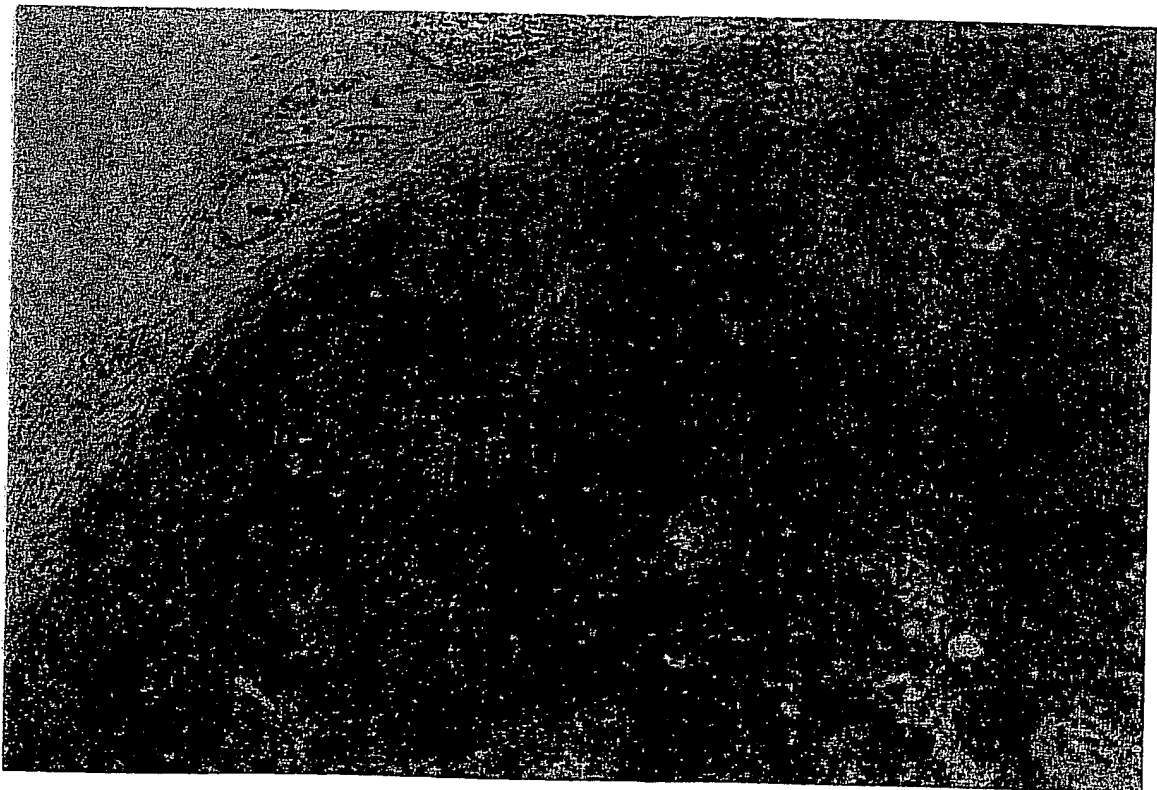
Fig. 51

Figure 7

A.



B.



00467593-440598

7=51

Fig. 52

| Time (day) | Incidence of Tumor Formation | | |
|---------------|------------------------------|--------------------|--------------------|
| | PBS | PK16.3.1 (1 mg) | E7.6.3 (0.2 mg) |
| | | | E7.6.3 (1 mg) |
| 0 | 0/5 | 0/5 | 0/10 |
| 3 | 4/5 | 0/5 | 0/10 |
| 8 | 4/5 | 3/5 | 0/10 |
| 10 | 5/5 | 5/5 | 0/10 |
| 25 | 5/5 | 5/5 | 0/10 |
| 100 | ND | ND | 0/10 |
| 250 | ND | ND | 0/10 |

00197593-110599

Table 1252

Fig. 53

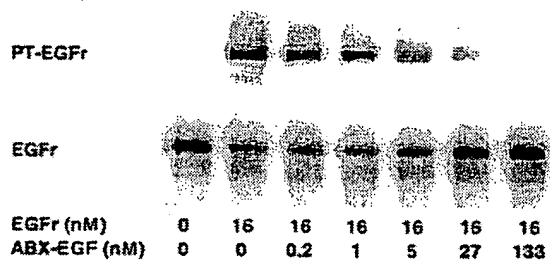
| Treatment (dose/injection) | Total Dose | Total No. of Mice | Tumor-free Mice on Day 60 | |
|-----------------------------------|------------|-------------------|---------------------------|-----|
| | | | No. | % |
| None | | 71 | 0 | 0 |
| Control IgG ₂ K (1 mg) | 6 mg | 16 | 0 | 0 |
| E7.6.3 (1 mg) | 6 mg | 50 | 50 | 100 |
| E7.6.3 (0.5 mg) | 3 mg | 20 | 19 | 95 |
| E7.6.3 (0.25 mg) | 1.5 mg | 5 | 3 | 60 |
| E7.6.3 (0.2 mg) | 1.2 mg | 19 | 5 | 26 |
| E7.6.3 (0.1 mg) | 0.6 mg | 20 | 13 | 65 |
| E7.6.3 (0.05 mg) | 0.3 mg | 15 | 1 | 7 |

00197593-110599

Table 2-53

B7.6.3

Inhibitory Effects of ~~ABX-EGF~~ on EGF-induced
Tyrosine-phosphorylation and Degradation of EGFr in
Cultured A431 Cells

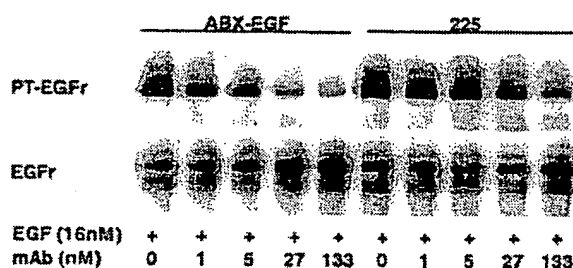


A

00197593 110599

Preliminary Results Obtained Comparing

Inhibitory Effects of ~~ABX-EGF~~^{EGF 16.3} and 225 on EGF-induced Tyrosine-phosphorylation and Degradation of EGFr in Cultured A431 Cells



A

00197503-110500

Preliminary Results Obtained Comparing

Effects of EGF, ABX-EGF and 225 on
Tyrosine-phosphorylation and Degradation of EGFr in
Cultured A431 Cells

PT-EGFr

EGFr

| | | | | | | | | | | | | |
|-----------------|---|---|---|-----|-----|-----|----|----|----|-----|-----|-----|
| EGF (nM) | 0 | 0 | 0 | 1.6 | 1.6 | 1.6 | 16 | 16 | 16 | 160 | 160 | 160 |
| ABX-EGF (133nM) | - | + | - | - | + | - | - | + | - | - | + | - |
| 225 (133nM) | - | - | + | - | - | + | - | - | + | - | - | + |

00497503-10000

| 10 | 20 | 30 | 40 | 50 | |
|-------------------------|-----------------------|------------------------|-----------------------|-----------------------|-----|
| 1234567890 | 1234567890 | 1234567890 | 1234567890 | 1234567890 | |
| GCGATCCAGC | CTTTTAGGTC | CATGCCNTTC | TCCTGIGNAG | CGTCTGGATT | 50 |
| A I Q P | F R S | M P F | S C X A | S G F | |
| CCCCITCAGT | AGNINIGGCA | TGCACTGGGT | CCGCCAGGCT | CCAGGCAAGG | 100 |
| P F S | X X G M | H W V | R Q A | P G K G | |
| GGCTGGAGTG | GGTGGCAGTT | ATATGGTATG | ATGGAAGTAA | TAAATACTAT | 150 |
| L E W | V A V | I W Y D | G S N | K Y Y | |
| GCAGACTCCG | TGAAGGGCCG | ATTCAACATC | TCCAGAGACA | ATTCCAAGAA | 200 |
| A D S V | K G R | F T I | S R D N | S K N | |
| CACGCTGTAT | CTGCAATGA | ACAGACTGAG | AGCCGAGGAC | ACGGCTGTGT | 250 |
| T L Y | L Q M N | R L R | A E D | T A V Y | |
| ATTACTGIGC | GACATTTTC | GACGCGTATC | CGTTTTCAGT | ATGCGGCGAC | 300 |
| Y C A | R F L | E W L P | F D Y | W G Q | |
| CGAACCCTGGCT | TCACCGTATC | CTCAGCACTCC | ACCAAGGGCC | CATCGGTCTT | 350 |
| G T L V | T V X | S D S | T K G P | S V F | |
| CNCCCTGGCG | CCCTGCTTCC | AGGAGCACCC | TCNGANAGCA | CANANGGCC | 400 |
| X L A | P C F Q | E H P | X X A | X X A P | |
| CTGGGACTGN | CTGNTACAAG | GACTINCTTC | CCTCNAACCN | GGTGACCNIN | 450 |
| G T X | X Y K | D X F P | S N X | V T X | |
| TCNTGGGAAA | CTCAGNGCNC | NTCTNNATNA | C | | 481 |
| S W E T | Q X X | S X X | | | |

00197503-110500

SECRET
REF ID: A66544

[illegible]

DNI: ~~1234~~

[illegible]

E20.8.1MG30.Seq Sequence

sp 30/10/20
D
J JH4b Fig. 61

| 10 | 20 | 30 | 40 | 50 | |
|------------|------------|-------------------|------------|------------|-----|
| 1234567890 | 1234567890 | 1234567890 | 1234567890 | 1234567890 | |
| CNGCCTGTIA | GGTCNTGCG | ACTCTCCTGT | GCAGCGTCTG | GATTCATCTT | 50 |
| X P V R | S X R | L S C | A A S G | F I F | |
| CAGTAGNTAT | GGCATGCACT | GGGTCCGCCA | GGCTCCAGGC | AAGGGGCTGG | 100 |
| S X Y | G M H W | V R Q | A P G | K G L E | |
| AGTGGGTGGC | AATTATATGG | TATGATGGAA | GTAATAAATA | CTATGCAGAC | 150 |
| W V A | I I W | Y D G S | N K Y | Y A D | |
| TCCGTGAAGG | GCCGATTCAC | CATCTCCAGA | GACAATTCCA | AGAACACGCT | 200 |
| S V K G | R F T | I S R | D N S K | N T L | |
| GTATCTGCAA | ATGAACAGCC | TGAGAGCCGA | GGACACGGCT | GIGIATTACT | 250 |
| Y L Q | M N S L | R A E | D T A | V Y Y C | |
| GTCGAGAGA | CGGGGGGCCA | <u>CGGIGGTTTC</u> | TGCCTTCTGA | CTACTGGGGC | 300 |
| A R D | G G P | R W F L | A S D | Y W G | |
| CAGGGAACCC | TGGTCACCGT | CTCCTCAGCC | TCCACCAAGG | GCCCATCGGT | 350 |
| Q G T L | V T V | S S A | S T K G | P S V | |
| CTTCCCCCTG | GCGCCCTGCT | CCAGGAGCAC | CCTTCGAGAG | CACAGCGGCC | 400 |
| F P L | A P C S | R S T | L R E | H S G P | |
| CTGGGCTGCC | TGGTCAAGG | ACTACTTTCC | CCGAACCGGT | GACGGTGINC | 450 |
| G L P | G S R | T T F P | E P V | T V X | |
| GTGGAACTC | ATGAC | | | | 465 |
| V G T H | D | | | | |

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| 10 | 20 | 30 | 40 | 50 | |
|------------|------------|------------|------------|-------------|-----|
| 1234567890 | 1234567890 | 1234567890 | 1234567890 | 1234567890 | |
| AGTCTCCAGA | CTCCCTGGTT | GTGTCTCTGG | GCGAGAGGGC | CACCATCAAC | 50 |
| S L Q T | P W L | C L W | A R G P | P S T | |
| TGCAAGTCCA | GNCAGAGTAT | TTTATACAGC | TCCAACAATC | AAAAACTTCT | 100 |
| A S P | X R V F | Y T A | P T I | K N F L | |
| TAGCTTGGTA | CCAGCAGAAA | CCAGGACAGC | CTCCGAAGTT | GCTCATTTC | 150 |
| A W Y | Q Q K | P G Q P | P K L | L I Y | |
| TGGGCATCTA | TTGGGGAATC | CGGGGTCCCT | GACCGATTCA | GTGGCAGCGG | 200 |
| W A S I | R E S | G V P | D R F S | G S G | |
| GTCTGGGACA | GATTTCACTC | TCACCATCAG | CAGCCTGCAG | GCTGAAGATG | 250 |
| S G T | D F T L | T I S | S L Q | A E D V | |
| TGGCAGTTTA | TTACTGTCAG | CAGTATTATA | GTATTCCGTG | CACTTTITGGC | 300 |
| A V Y | Y C Q | Q Y Y S | I P C | T F G | |
| CAGGGGACCA | AGCTGGAGAT | CAAACGAACT | GTGGCTGCAC | CATCTGTCTT | 350 |
| Q G T K | L E I | K R T | V A A P | S V F | |
| CATCTTCCCG | CCATCTGATG | AGCAGTTGAA | ATCTGGAACT | GCCTCTGTGTG | 400 |
| I F P | P S D E | Q L K | S G T | A S V V | |
| TGTGCCTGCT | GAATAACTTC | TATCCCAGAA | AGGCCAAAGT | ACATGAAGGG | 450 |
| C L L | N N F | Y P R K | A K V | H E G | |
| TTCAAA | | | | | 456 |
| F K | | | | | |

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[illegible]

E20.18MG30.Seq Sequence

D-
J- Fig. 65

| 10 | 20 | 30 | 40 | 50 | |
|------------|------------|------------|------------|------------|-----|
| 1234567890 | 1234567890 | 1234567890 | 1234567890 | 1234567890 | |
| CGTGATCCNC | CTGGNIGGTC | CCTGAGACTC | TCCTGIGCAG | CGTCTGGATT | 50 |
| R D P P | G W S | L R L | S C A A | S G F | |
| CATCTTCANT | AACTATTNCA | TGCACTGGGT | CCGCCAGGCT | CCAGGCAAGG | 100 |
| I F X | N Y X M | H W V | R Q A | P G K G | |
| GGCTGGAGTG | GGTGGCAATT | ATATGGTATG | ATGGAAGTAG | CAAATACTAT | 150 |
| L E W | V A I | I W Y D | G S S | K Y Y | |
| GCAGACTCCG | NGAAGGGCCG | ATTCACCATC | TCCAGAGACA | ATTCCAAGAA | 200 |
| A D S X | K G R | F T I | S R D N | S K N | |
| CACGCTGTAT | CTGCAAATGA | ACAGCCTGAG | AGCCGAGGAC | ACGGCTGATG | 250 |
| T L Y | L Q M N | S L R | A E D | T A D V | |
| TATTACTGTG | CGAGAGACGG | TTGGGCCACG | GTGGCTTCTC | GCTTCTGACT | 300 |
| L L C | E R R | L G H G | G F S | L L T | |
| ACTGGNGCNC | AGGGCAACNC | TGNCINACCG | TNTTCCTCAN | CCCINTACNC | 350 |
| T G A Q | G N X | X X P | X S S X | L Y X | |
| AAGGGCCNCC | ATINGGTCTT | TCCCCCCTGG | NNNNCCTGCT | CNATGNNNCA | 400 |
| R A X | I X S F | P P G | X P A | X X X T | |
| CCCINCGACA | NCNACAN | | | | 417 |
| L R X | X X | | | | |

00107503-110500

E20.18VK.Seq Sequence

J-JK2 Fig. 66

| 10 | 20 | 30 | 40 | 50 | |
|------------|------------|-------------|------------|------------|-----|
| 1234567890 | 1234567890 | 1234567890 | 1234567890 | 1234567890 | |
| TTCGIGGCTG | TGTCCTCTGG | CGACAGGNCC | ACCATCAACT | GCAAGTCCAG | 50 |
| F V A V | S L G | E R X | T I N C | K S S | |
| CCAGAGTATT | TTATACAGCT | CCAACAATCA | AAACTTCTTA | GCTTGGTACC | 100 |
| Q S I | L Y S S | N N Q | N F L | A W Y Q | |
| AGCAGAAACC | AGGACAGCCT | CCGAAGTTGC | TCATTTACTG | GGCATCTATT | 150 |
| Q K P | G Q P | P K L L | I Y W | A S I | |
| CGGGAATCCG | GGGTCCCTGA | CCGATTTCAGT | GGCAGCGGGT | CTGGGACAGA | 200 |
| R E S G | V P D | R F S | G S G S | G T D | |
| TTTCACTCTC | ACCATCAGCA | GCCTGCAGGC | TGAAGATGTG | GCAGTTTATT | 250 |
| F T L | T I S S | L Q A | E D V | A V Y Y | |
| ACTGTCAGCA | GTATTATAGT | ATTCGGTGCA | CTTTTGGCCA | GGGGACCAAG | 300 |
| C Q Q | Y Y S | I P C T | F G Q | G T K | |
| CTGGAGATCA | AACGAACTGT | GGCTGCACCA | TCTGTCTTCA | TCTTCCCGCC | 350 |
| L E I K | R T V | A A P | S V F I | F P P | |
| ATCTGATGAG | CCAAGNTTGA | AAATCTGGAA | CTGCCTCTGT | TGIGTGCCCT | 400 |
| S D E | P X L K | I W N | C L C | C V P C | |
| GCTTGAATAA | CTTCTATCCC | AGAGANGGCC | AAAGTCCNGT | GGAAGGTGGA | 450 |
| L N N | F Y P | R X G Q | S P V | E G G | |
| TAC | | | | | 453 |
| Y | | | | | |

00197503-110500

| 10 | 20 | 30 | 40 | 50 | |
|------------|-------------|------------|------------|------------|-----|
| 1234567890 | 1234567890 | 1234567890 | 1234567890 | 1234567890 | |
| CTCACCTGCA | CTGTCCTG | TGGCTCCATC | AGTAGTTACT | NTTGGAGNTG | 50 |
| L T C T | V S G | G S I | S S Y X | W X W | |
| GATCCGGCAG | CCCGNAGGGA | AGGGACTGGA | GTGGATTGGG | TGTTTCTATT | 100 |
| I R Q | P X G K | G L E | W I G | C F Y Y | |
| ACAGNGGGAG | CACCAACTAC | AACCCCTCCC | TNAAGAGTCA | TGTCACCATA | 150 |
| X G S | T N Y | N P S L | K S H | V T I | |
| TCAGTAGACA | CGTCCAAGAA | CCAGTTCTAC | NIGAAGCTGA | GCINTGTGAC | 200 |
| S V D T | S K N | Q F Y | X K L S | X V T | |
| CGNTGCGGAC | ACGNGCGNGA | ATAACTGNGC | NAGAGATAGG | GGAGNAGTGN | 250 |
| X A D | T X X N | N X A | R D R | G X V X | |
| NNIGGCNINC | TACTINTGACT | ACTGAGGCCA | GNGAACCNTG | GNICACAGTA | 300 |
| W X X | T X T | T E A X | E P W | X T V | |
| ATCCNTAAGN | CTNNCAANCA | AANGNGNCCC | AANGNGANAC | NINNCINCN | 350 |
| I X K X | X X Q | X X P | X X X X | X X | |

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JK - JKI
Fig. 68

| Year | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 | 2032 | 2033 | 2034 | 2035 | 2036 | 2037 | 2038 | 2039 | 2040 | 2041 | 2042 | 2043 | 2044 | 2045 | 2046 | 2047 | 2048 | 2049 | 2050 | 2051 | 2052 | 2053 | 2054 | 2055 | 2056 | 2057 | 2058 | 2059 | 2060 | 2061 | 2062 | 2063 | 2064 | 2065 | 2066 | 2067 | 2068 | 2069 | 2070 | 2071 | 2072 | 2073 | 2074 | 2075 | 2076 | 2077 | 2078 | 2079 | 2080 | 2081 | 2082 | 2083 | 2084 | 2085 | 2086 | 2087 | 2088 | 2089 | 2090 | 2091 | 2092 | 2093 | 2094 | 2095 | 2096 | 2097 | 2098 | 2099 | 2100 |
|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 | 2032 | 2033 | 2034 | 2035 | 2036 | 2037 | 2038 | 2039 | 2040 | 2041 | 2042 | 2043 | 2044 | 2045 | 2046 | 2047 | 2048 | 2049 | 2050 | 2051 | 2052 | 2053 | 2054 | 2055 | 2056 | 2057 | 2058 | 2059 | 2060 | 2061 | 2062 | 2063 | 2064 | 2065 | 2066 | 2067 | 2068 | 2069 | 2070 | 2071 | 2072 | 2073 | 2074 | 2075 | 2076 | 2077 | 2078 | 2079 | 2080 | 2081 | 2082 | 2083 | 2084 | 2085 | 2086 | 2087 | 2088 | 2089 | 2090 | 2091 | 2092 | 2093 | 2094 | 2095 | 2096 | 2097 | 2098 | 2099 | 2100 | |

69
Fig. 69

[illegible]

| 10 | 20 | 30 | 40 | 50 | |
|------------|-------------------|------------|------------|------------|-----|
| 1234567890 | 1234567890 | 1234567890 | 1234567890 | 1234567890 | |
| AAGCCTTTTC | AGACCTTGCC | CTTCACCTGC | ACTGTCTCTG | GTGGCTCCAT | 50 |
| K P F Q | T X P | F T C | T V S G | G S I | |
| CAGCAGTGGT | GGTIACTACT | GGAGCTGGAT | CCGCCAGCAC | CCAGGGAAGG | 100 |
| S S G | G Y Y W | S W I | R Q H | P G K G | |
| GCCTGGAGTG | GATTGGGTAC | ATCTATAACA | GTGGGAGCAC | CTACTACAAC | 150 |
| L E W | I G Y | I Y N S | G S T | Y Y N | |
| CCGTCCCTCC | AGAGTCGAGT | TACCATATCA | GTAGACACGT | CTAAGAACCA | 200 |
| P S L Q | S R V | T I S | V D T S | K N Q | |
| GTCTCCCTG | AAGCTGAGCT | CTGTGACTGC | CGCGGACACG | GCCGTGTATT | 250 |
| F S L | K L S S | V T A | A D T | A V Y Y | |
| ACTGTGCGGG | <u>TCAGAAATGG</u> | TCCTACTACT | ACTACTACGG | TATGGACGTC | 300 |
| C A G | Q K W | S Y Y Y | Y Y G | M D V | |
| TGGGGCCAAG | GGACCACGGT | CACCGTCTCC | TNAGCCTCCA | CCAANGGCCC | 350 |
| W G Q G | T T V | T V S | X A S T | X G P | |
| ATCGGTCTTC | CCCCGCGC | CCTGNTCTAG | GAGCACCTCC | CANAGCACAG | 400 |
| S V F | P L A P | X S R | S T S | X S T D | |
| ACGGATNCTG | GGCCTGCCTG | NATCAATGGA | CTACTTTCCC | CGAACCGGTT | 450 |
| G X W | A C L | X Q W T | T F P | E P V | |
| GNNIGTGNNN | CCTGGNAACT | N | | | 471 |
| X C X X | W X L | | | | |

Amino Acid Sequences and Structure of Human Heavy Chain Derived from EGFR-Specific Hybridomas

| Human $\gamma 2$ | CDR1 | CDR2 | CDR3 | ASTKGPSVFPPLAPCSRSTST |
|------------------|--|----------------------------------|----------------|-----------------------|
| 4-31 | VSGGSISGGYYWSWIRQHPGKGLEWIGYIYSGSTNYNPSLKS | RVVTISVDTSKNQFSLKLSVTAADTAVYYCAR | STVNPNG WFDPP | WGQGTLLVTVSS |
| E2.1 | N-D | DC | F-T | WGQGTLLVTVSS |
| E2.4 | N-D | S-N-F | L | WGQGTLLVTVSS |
| E2.5 | D-T | N | SM-I-E | WGQGTLLVTVSS |
| E6.2 | N-DF | N | M-I-P | WGQGTLLVTVSS |
| E6.4 | NN-D | H-I | T-N | WGQGTLLVTVSS |
| E20.21 | C | N-Q | GKWSYYYYYGMDDV | WGQGTLLVTVSS |
| 4-61 | VSGGSVSGSYTWSWIRQPPGKGLEWIGYIYSGSTNYNPSLKS | RVVTISVDTSKNQFSLKLSVTAADTAVYYCAR | DFLTGSF FDY | WGQGTLLVTVSS |
| E2.11 | D | HL-N | L | WGQGTLLVTVSS |
| E6.3 | Y-D | N | DSILGA TNY | WGQGTLLVTVSS |
| E7.6.3 | D-T-S | H-N | L-I-T | WGQGTLLVTVSS |
| | | | I-V-DRVTGA FDI | WGQGTLLVTVSS |

Figure 71

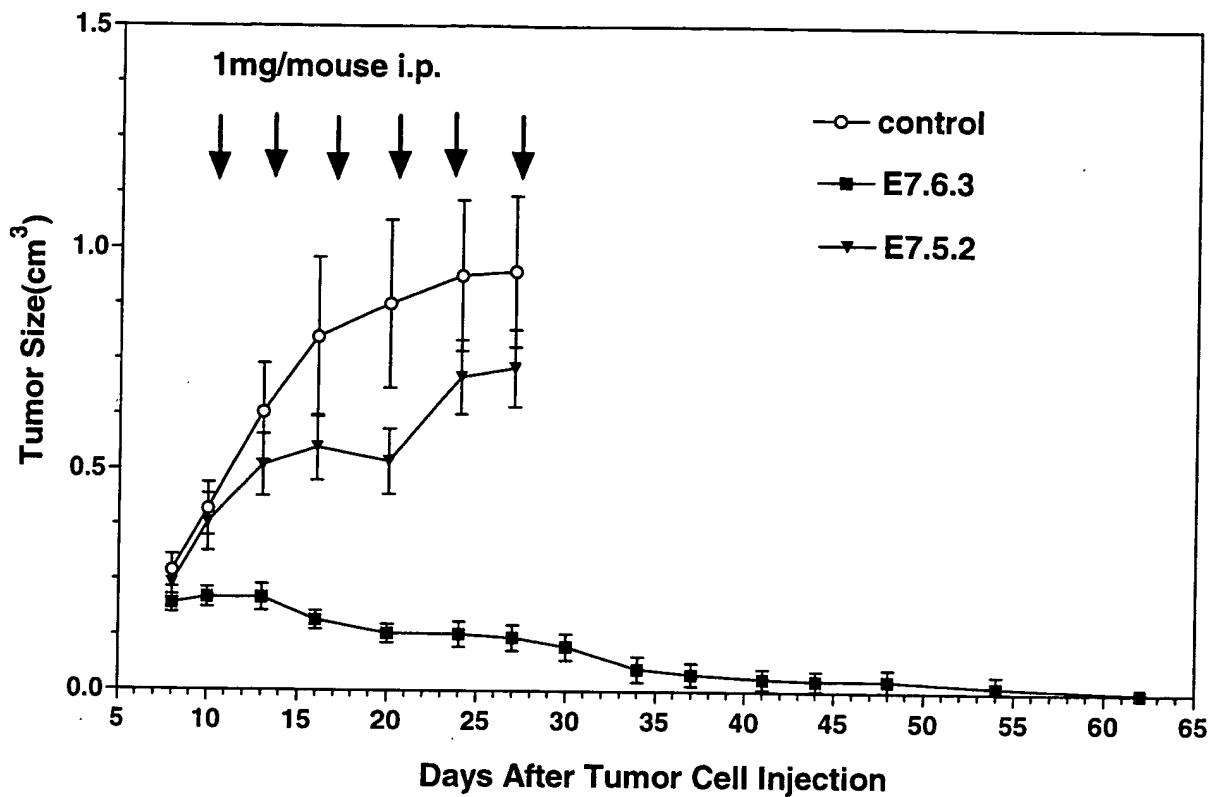
1000
900
800
700
600
500
400
300
200
100
0

| 10 | 20 | 30 | 40 | 50 | |
|-------------|------------|------------|-------------|------------|-----|
| 1234567890 | 1234567890 | 1234567890 | 1234567890 | 1234567890 | |
| CTGTCCTGCAT | CTGTAGGAGA | CAGAGTCATA | ATCACTTGCC | GGGCAAGTCA | 50 |
| L S A S | V G D | R V I | I T C R | A S Q | |
| AAACATCACC | GACCATTTAA | ATTGGTATCA | GCAGATAGCA | GGAAAAGCCC | 100 |
| N I T | D H L N | W Y Q | Q I A | G K A P | |
| CTAGGCCCCCT | GATATACACT | GCATCCAGTT | TGCAAGGTGG | GGTCCCATCA | 150 |
| R P L | I Y T | A S S L | Q G G | V P S | |
| AGGTTTCAGTG | GCAGTGGATC | TGGGACAGAT | TTCACCTCTCA | CCATCAGCAG | 200 |
| R F S G | S G S | G T D | F T L T | I S S | |
| TCTGCAACCT | GAAGATTTTT | CAACTTACTA | CTGTCAACAG | AGTTACAGTA | 250 |
| L Q P | E D F S | T Y Y | C Q Q | S Y S T | |
| CCCCGTGCAG | TTTTGGCCAG | GGGACCAAGC | TGGAGATCAA | ACGAACTGTG | 300 |
| P C S | F G Q | G T K L | E I K | R T V | |
| GCTGCACCAT | CTGTCTTCAT | CTTCCCGCCA | TCTGATGAGC | AGTTGAAATC | 350 |
| A A P S | V F I | F P P | S D E Q | L K S | |
| TGGAACCTGCC | TCTGTTGTGT | GCCTGCTGAA | TAACTTCTAT | CCCA | 394 |
| G T A | S V V C | L L N | N F Y | P | |

| 10 | 20 | 30 | 40 | 50 | |
|------------|------------|------------|------------|------------|-----|
| 1234567890 | 1234567890 | 1234567890 | 1234567890 | 1234567890 | |
| GTGAAGGICT | CCTGCAAGGC | TTCTGGATAC | ACCTTCAGCG | GCTACTATAT | 50 |
| V K V S | C K A | S G Y | T F S G | Y Y M | |
| | | | | | |
| GCACTGGGTG | CGACAGGCC | CTGGACAAGG | GCTTGAGTGG | ATGGGATCGA | 100 |
| H W V | R Q A P | G Q G | L E W | M G S I | |
| | | | | | |
| TCCACCCTAA | CAGTGGTGGC | ANAACTTTG | CACAGAAGTT | TCAGGGCAGG | 150 |
| H P N | S G G | X N F A | Q K F | Q G R | |
| | | | | | |
| GTCACCATGA | CCAGGGACAC | GTCCATCAAC | ACAGCCTACT | TGGAGCTGAG | 200 |
| V T M T | R D T | S I N | T A Y L | E L S | |
| | | | | | |
| CAGGCTGAGA | TCTGACGACA | CGGCCGIGTA | TTACTGTGCG | AGAGATAAAA | 250 |
| R L R | S D D T | A V Y | Y C A | R D K N | |
| | | | | | |
| ACTACGGTGA | CTACGICTTT | GACTATTGGG | GCCAGGGAAC | CCTGGTCACC | 300 |
| Y G D | Y V F | D Y W G | Q G T | L V T | |
| | | | | | |
| GTCTCCTCAG | | | | | 310 |
| V S S | | | | | |

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74
Figure 1 Effect of E7.6.3 or E7.5.2 on human epidermoid carcinoma A431 growth in nude mice



75
Figure 8. Effect of E7.6.3 on human pancreatic carcinoma HPAC growth in nude mice

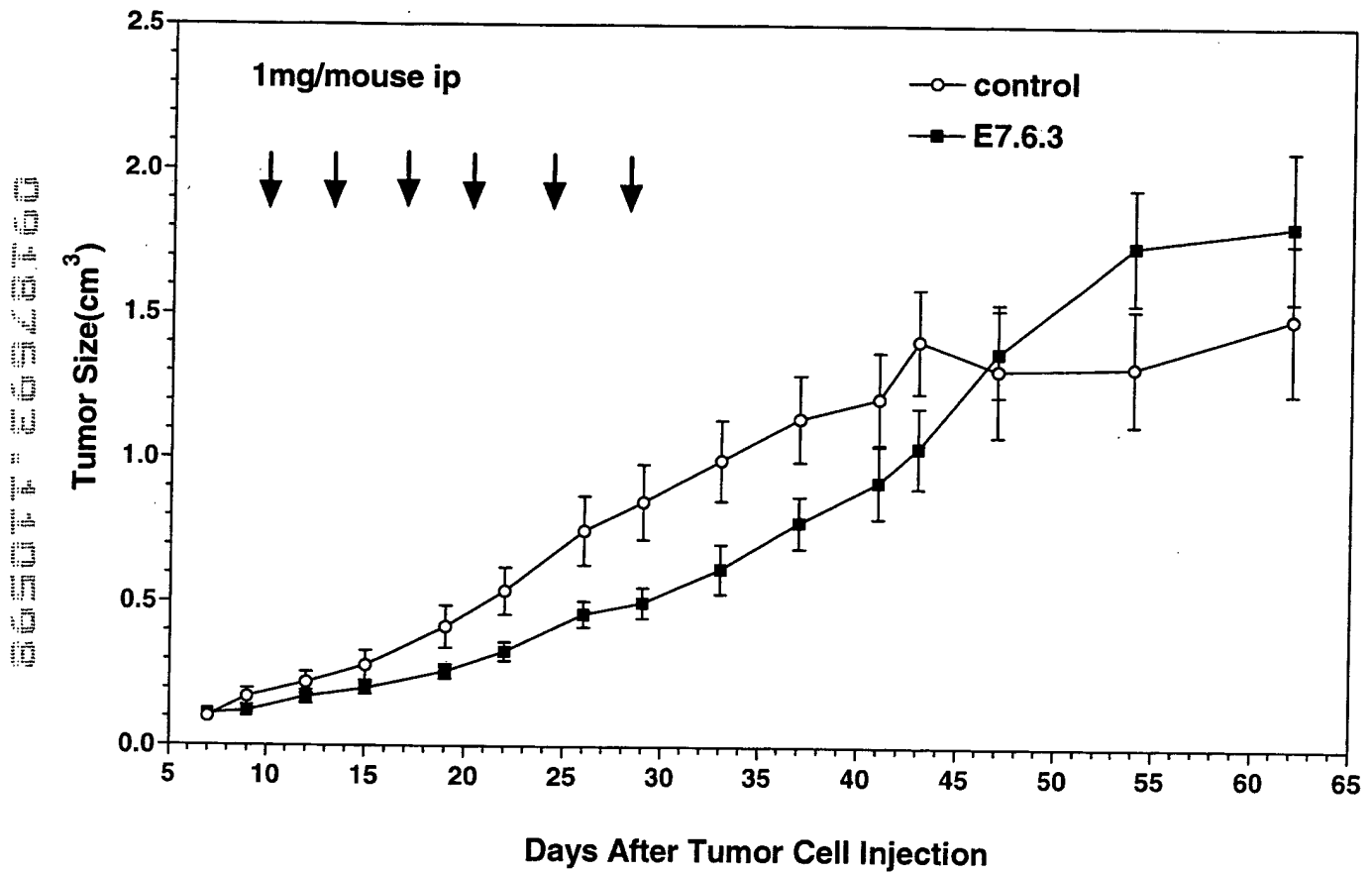


Figure 76 Effect of E7.6.3 on human pancreatic carcinoma BxPC-3 growth in nude mice

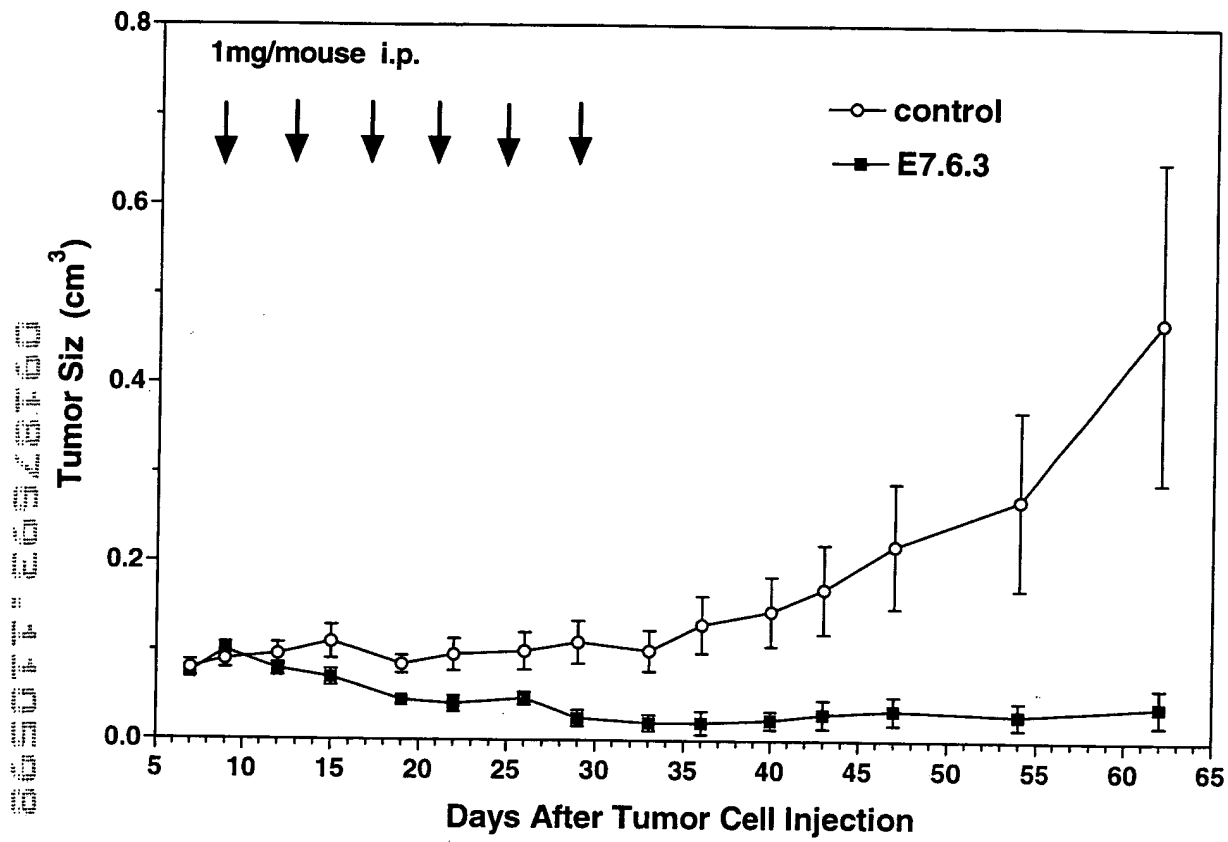
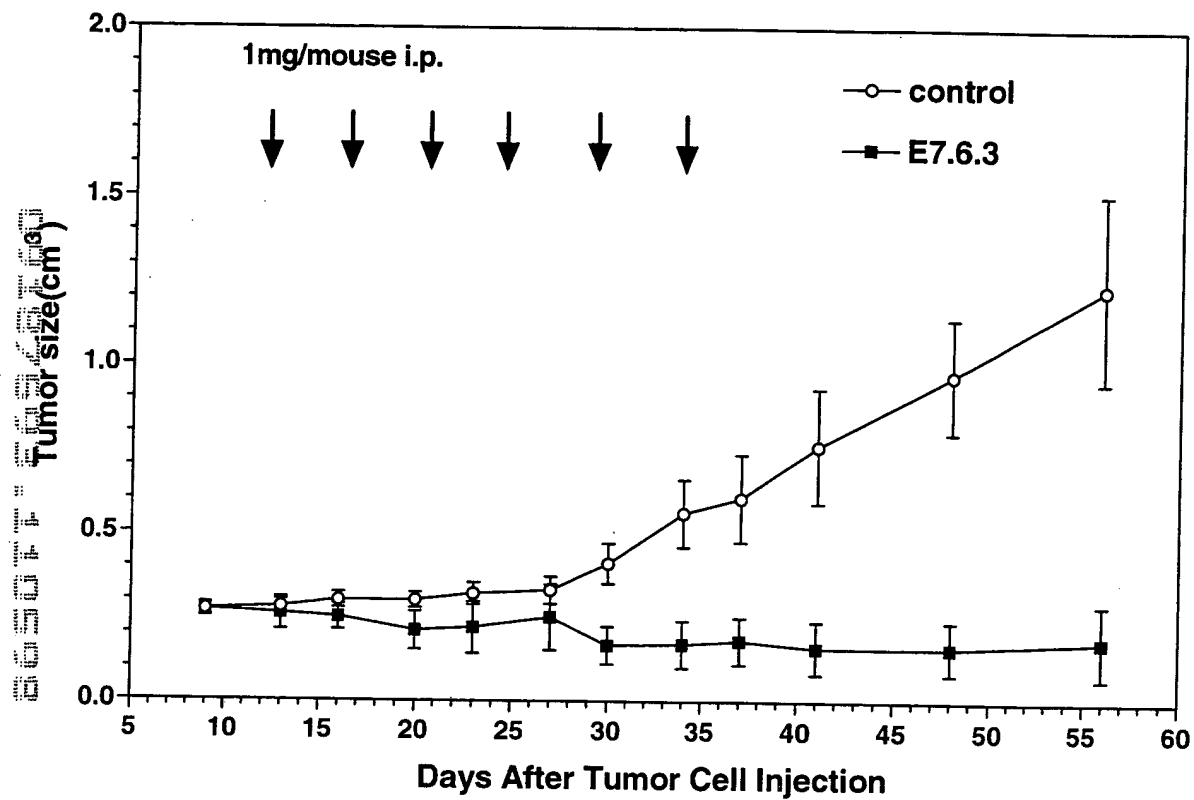


Figure 1 Effect of E7.6.3 on HS766T Pancreatic tumor growth in nude mice



78
Figure 2. Effect of E7.6.3 on SK-RC-29 human kidney carcinoma growth in nude mice

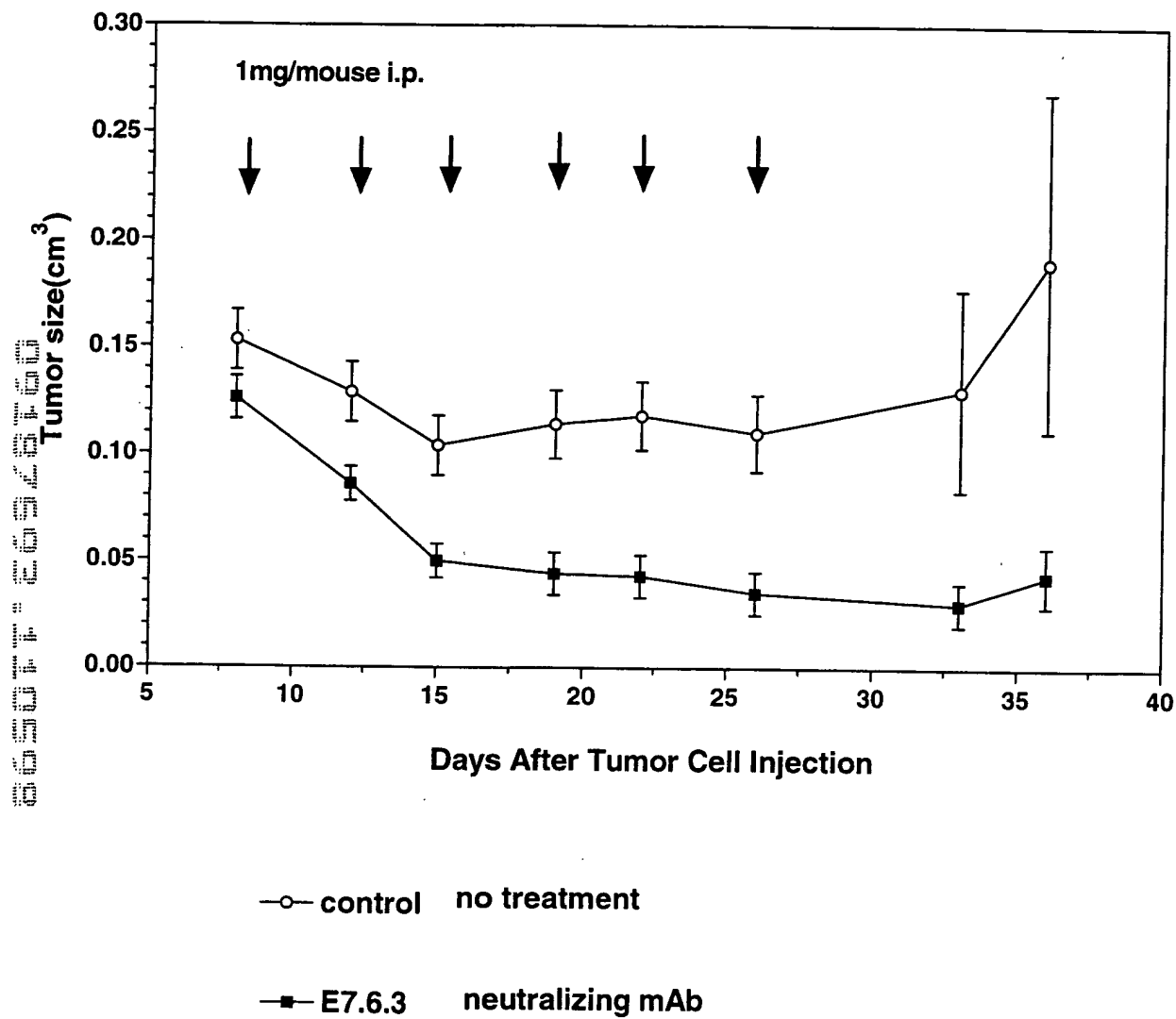


Figure ⁷⁹~~78~~ Effect of E7.6.3 on human colon carcinoma SW707 (EGFr⁻) growth in nude mice

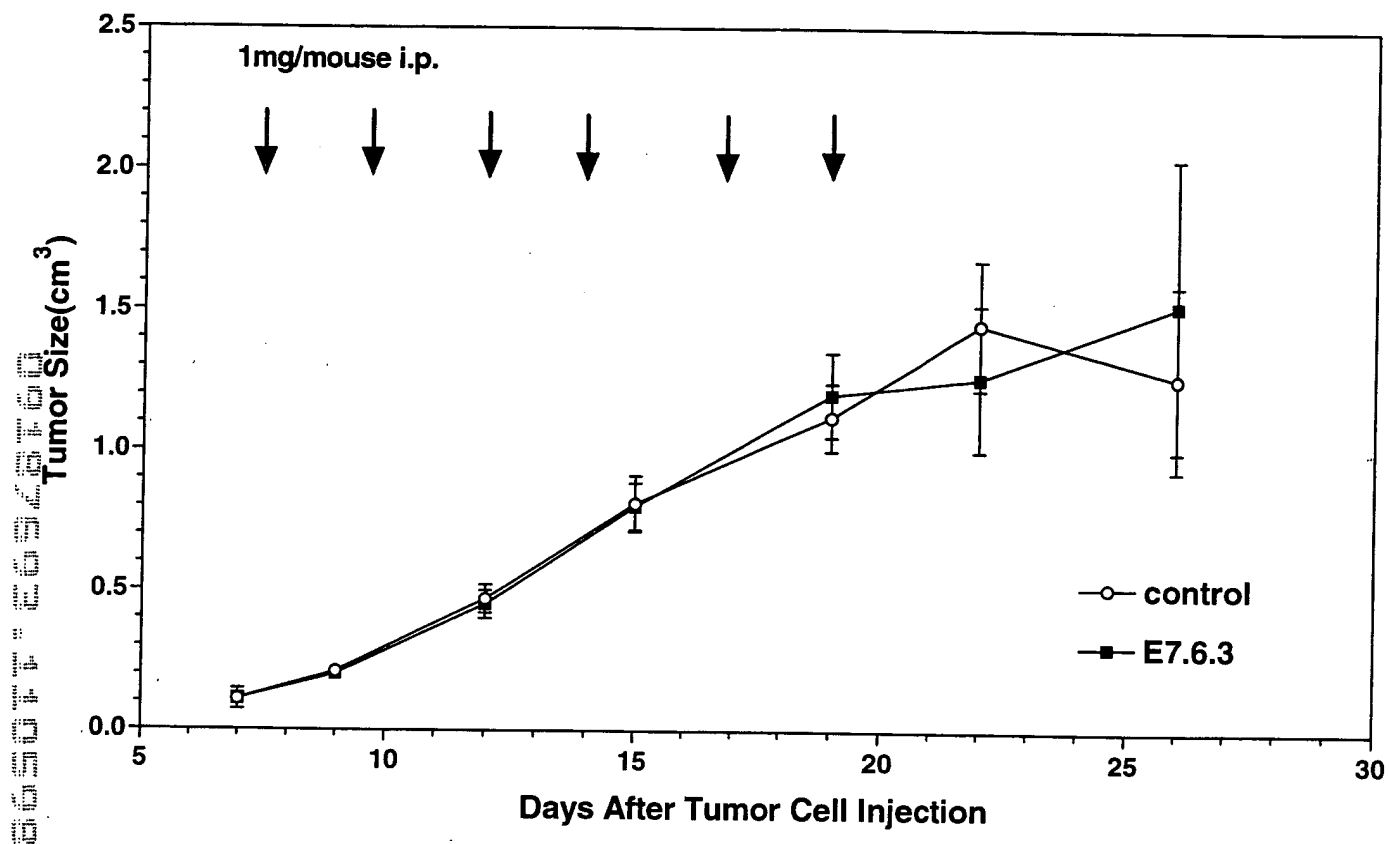
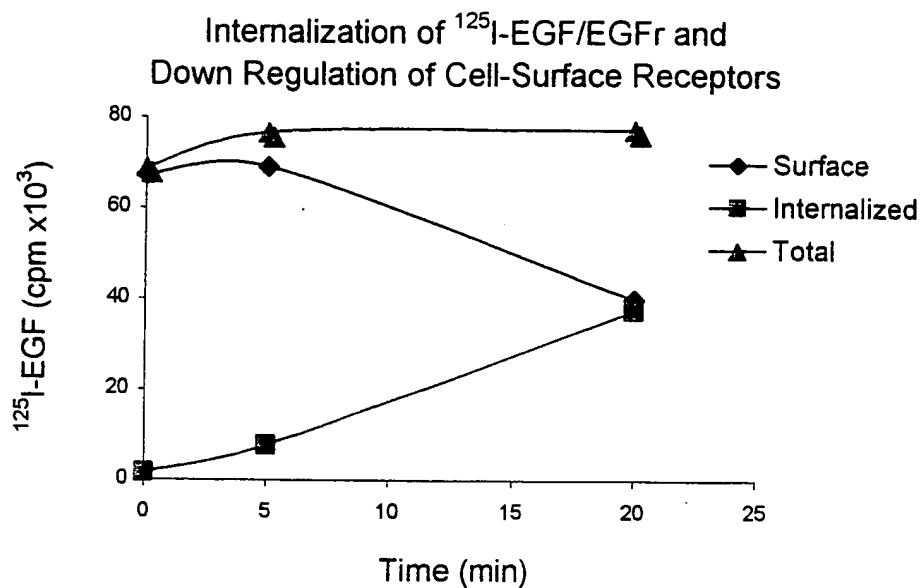


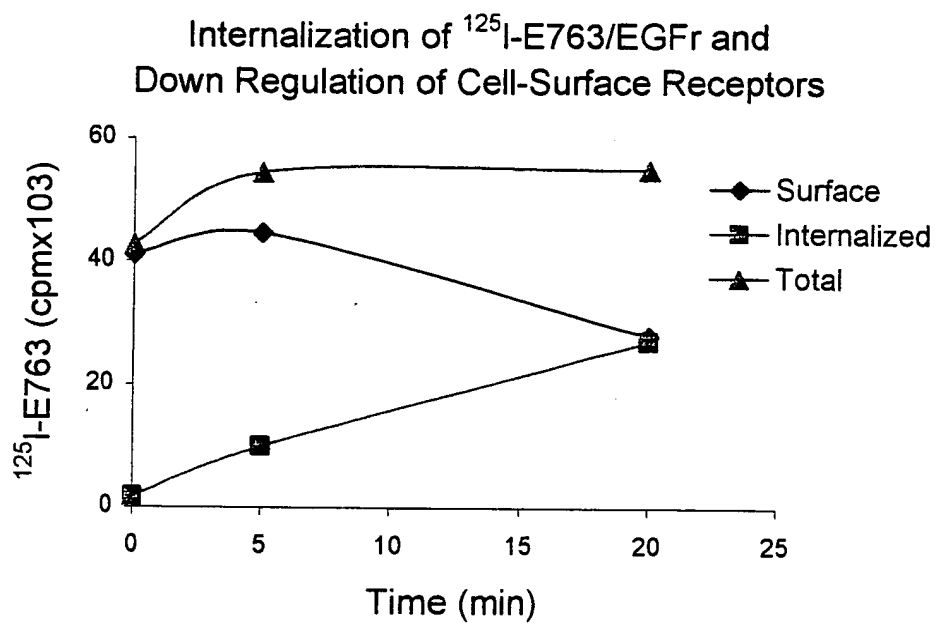
Figure 80



A

^{125}I -EGF

| Time (min) | Surface | Internalize | Total | % internalized |
|------------|---------|-------------|--------|----------------|
| 0 | 67.153 | 1.515 | 68.668 | 2.2 |
| 5 | 68.997 | 7.649 | 76.646 | 10 |
| 20 | 39.986 | 37.406 | 77.392 | 48 |



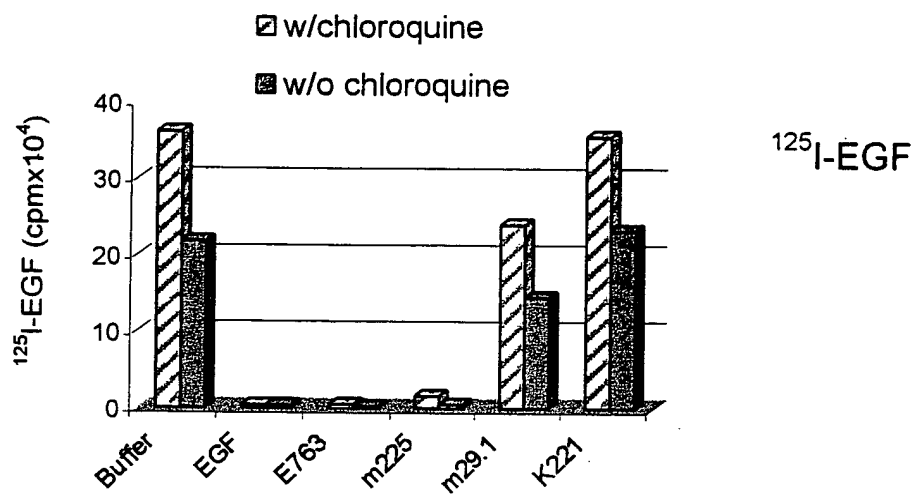
B

^{125}I -E763

| Time (min) | Surface | Internalize | Total | % internalized |
|------------|---------|-------------|--------|----------------|
| 0 | 41.051 | 1.684 | 42.735 | 3.9 |
| 5 | 44.567 | 9.876 | 54.443 | 18 |
| 20 | 27.969 | 26.998 | 54.967 | 49 |

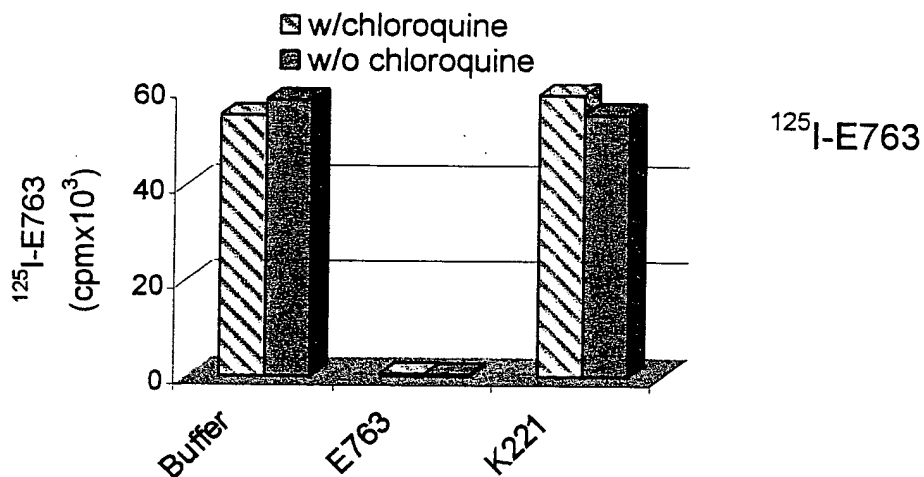
Figure 81

Degradation of ^{125}I -EGF or ^{125}I -E763 after binding to EGFr on A431 cell



w/ or w/o chloroquine (100 μM)

| cpm x 10 ⁴ | | w/chloroq | w/o chloroquine | % degradation | % competition |
|-----------------------|--------|-----------|-----------------|---------------|---------------|
| | Buffer | 36.0898 | 21.8277 | 40 | 0 |
| | EGF | 0.3684 | 0.3776 | | 98 |
| | E763 | 0.481 | 0.2132 | | 99 |
| | m225 | 1.5468 | 0.4882 | | 98 |
| | m29.1 | 23.9704 | 14.459 | | 34 |
| | K221 | 35.5084 | 23.2694 | 34 | 1.6 |



w/ or w/o chloroquine (100 μM)

| cpm x 10 ⁴ | | w/chloroq | w/o chloroquine | % degradation | % competition |
|-----------------------|--------|-----------|-----------------|---------------|---------------|
| | Buffer | 54.608 | 57.824 | 0 | 0 |
| | E763 | 0.536 | 0.441 | | 99 |
| | K221 | 58.956 | 54.83 | 7 | 5 |

[illegible]

Effects of E763 and m225 on EGFr degradation



Figure 83

Effects of E763 and m225 on EGFr threonine phosphorylation

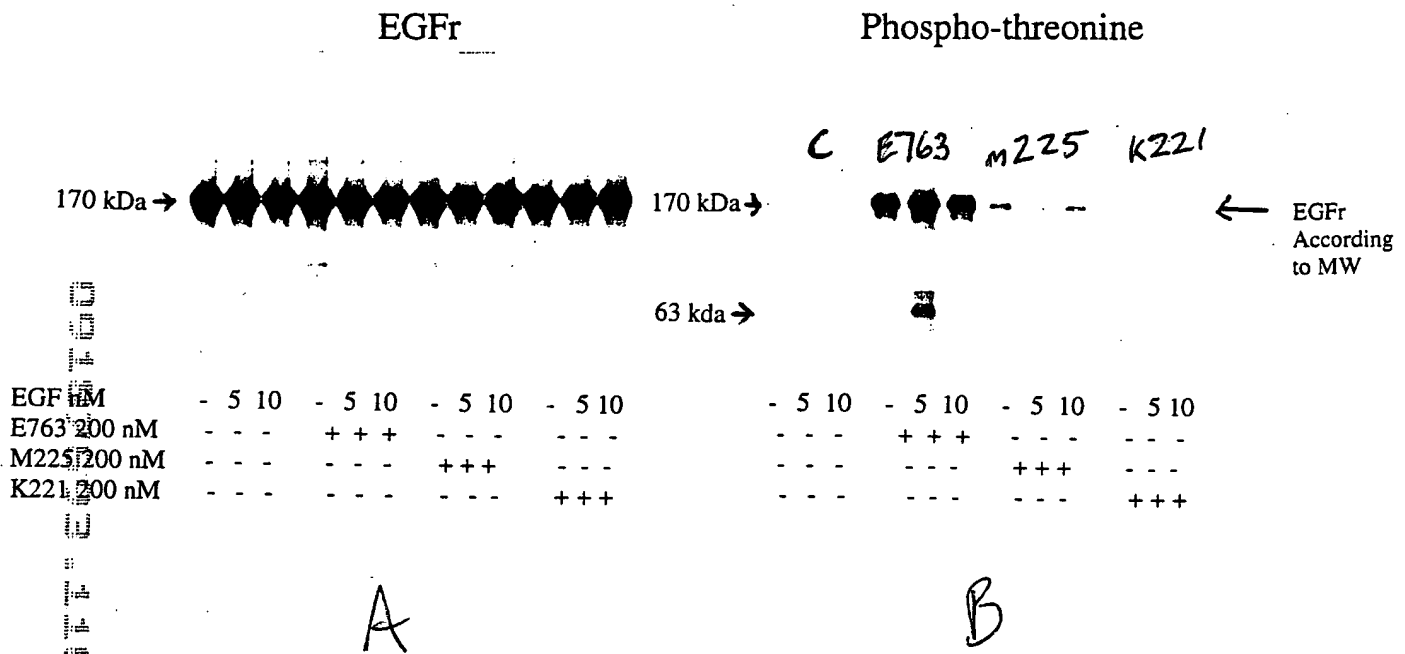
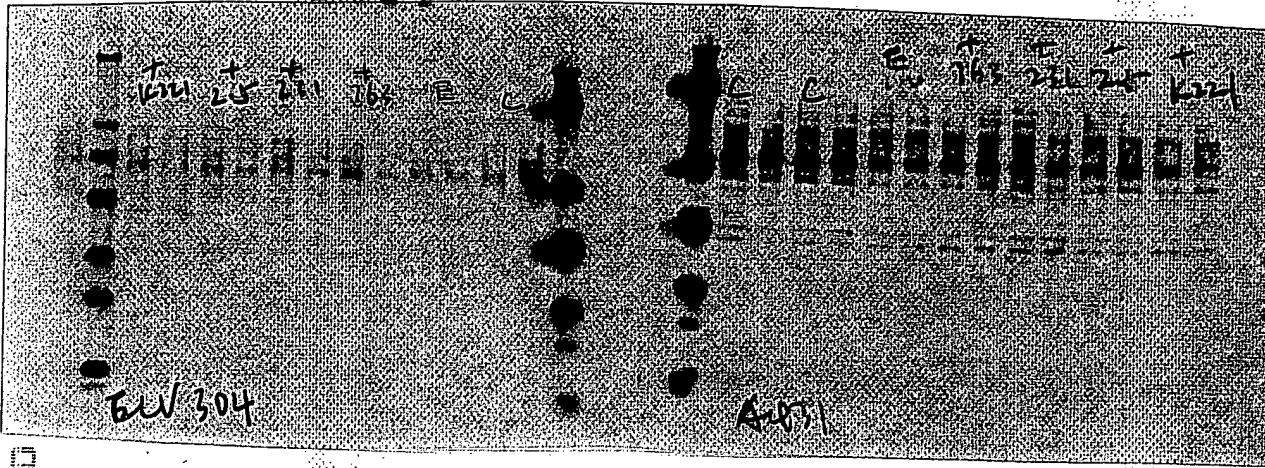


Figure 84

tyr. phos.
protocol
thr-phos
detect

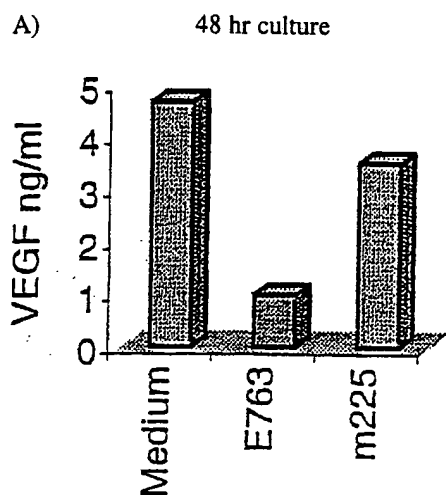


00197593 440500

E763 on VEGF secretion

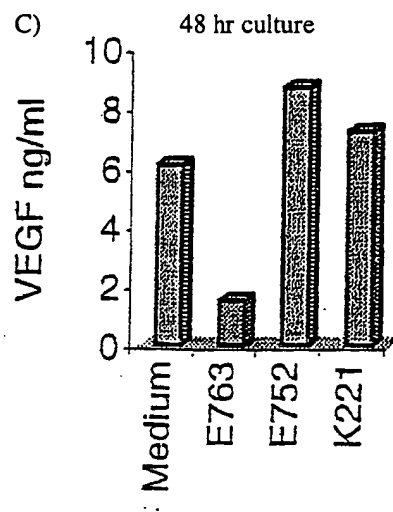
Figure 85

Effects of E763 and m225 on VEGF secretion in cultured A431 cells



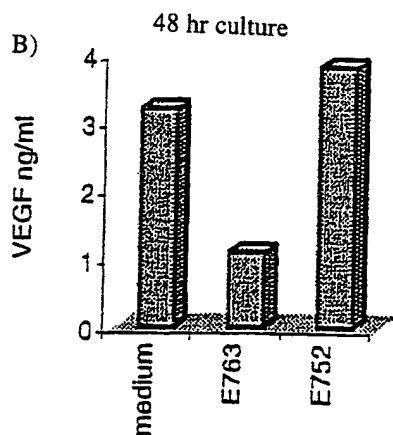
A

Effects of E763 and E752 on VEGF secretion in cultured A431 cells



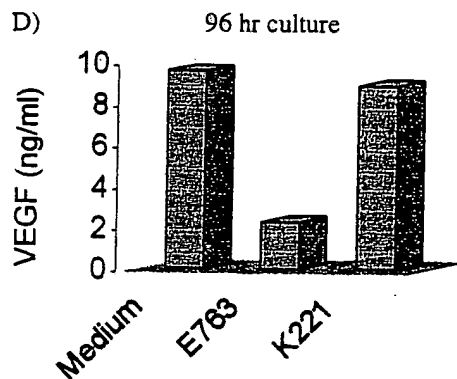
B

Effects of E763 and E752 on VEGF secretion in cultured A431 cells (24 hr)



C

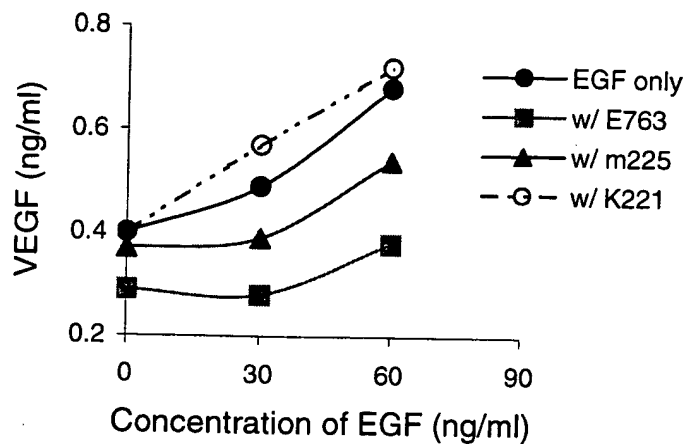
Effect of E763 on VEGF secretion in cultured A431 cells



D

Figure 8b

Effects of E763 and m225 on VEGF secretion in cultured endothelial cells



11/5/98 VEGF in endothelial cells (ECV304) (ATCC ; CRL-1998)

| | VEGF ng/ml | no serum | | |
|----------|------------|----------|------|--|
| | 0 | 30 | 60 | |
| EGF only | 0.4 | 0.49 | 0.68 | |
| w/ E763 | 0.29 | 0.28 | 0.38 | |
| w/ m225 | 0.37 | 0.39 | 0.54 | |
| w/ K221 | 0.4 | 0.57 | 0.72 | |

11/5/98 VEGF in endothelial cells (ECV304) (ATCC ; CRL-1998)